ORIGINAL ARTICLE

Anti-Spike antibodies 3 months after SARS-CoV-2 mRNA vaccine booster dose in patients on hemodialysis: the prospective SENCOVAC study

Borja Quiroga1, María José Soler2,3, Alberto Ortiz2,3, Carlos Jesús Jaravaca Mantecón5, Nathasha Nava Pérez5, Marta Serra Martín6, Yurika Sato6, Antonio José Marín Franco7, Diana Flor Pazmiño Zambrano7, Rafael Lucena Valverde8, Mayra Ortega Díaz8, Carmen Calderón González9, Juan Manuel Cazorla López10, Mónica Pereira4, Emilio González Parra4, Ana Sánchez Horrillo1, Carmen Sánchez González1, Néstor Toapanta2, Secundino Cigarrán Guldris11, Rosa Sánchez Hernández12, Soledad Pizarro Sánchez13, María Muñiz Rincón14, Nuria Garcia-Fernández15, Natalia Blanco Castro16, Rocío Collantes Mateo17, Manuel Augusto Quiroz Morales18, Beatriz Escamilla-Cabrera19, Isabel Berdud Godoy20, Beatriz Gil-Casares Casanova21, Alba Leyva22, José Rojas22, Ron T. Gansevoort23 and Patricia de Sequera3,8; on behalf of the SENCOVAC collaborative network*

1IIS-La Princesa, Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain, 2Nephrology Department, Vall d’Hebrón University Hospital, Barcelona, Spain, 3RICORS2040 (Kidney Disease), 4IIS-Fundación Jiménez Diaz, School of Medicine, Universidad Autónoma de Madrid, Fundación Renal Inigo Álvarez de Toledo-IRSIN, REDinREN, Instituto de Investigación Carlos III, Madrid, Spain, 5Diaverum Andalucía, Spain, 6Diaverum Valencia, Spain, 7Diaverum Castilla León-Galicia, Spain, 8Nephrology Department, Hospital Universitario Infantino Leonor – Universidad Complutense de Madrid, Madrid, Spain, 9Nephrology Department, Complejo Asistencial de Palencia, Palencia, Spain, 10Nephrology Department, Hospital Universitario Puerta del Mar, Cádiz, Spain, 11Nephrology Department, Hospital Da Mariña, Lugo, Spain, 12Nephrology Department, Hospital Universitario General de Villalba, Madrid, Spain, 13Nephrology Department, Hospital Rey Juan Carlos, Madrid, Spain, 14Nephrology Department, Hospital Clínico San Carlos, Madrid, Spain, 15Nephrology Department, Clínica Universidad de Navarra, Navarra, Spain, 16Nephrology Department, QuirónSalud A Coruña, A Coruña, Spain, 17Nephrology Department, Hospital Virgen de la Macarena, Sevilla, Spain, 18Nephrology Department, Consorci Sanitari Alt Penedés-Garraf, Barcelona, Spain, 19Nephrology Department, Hospital Universitario de Canarias, Canarias, Spain, 20FMC San Rafael, Córdoba, Spain, 21Nephrology

Received: 5.5.2022; Editorial decision: 24.6.2022

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Department, Hospital Universitario del Sureste, Madrid, Spain, 22R&D Department, VIRCELL SL, Granada, Spain and 23Dept Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

*The SENCOVAC collaborative network is listed in the Appendix.
Correspondence to: María José Soler; E-mail: mjsoler01@gmail.com; Alberto Ortiz; E-mail: aortiz@fjd.es

ABSTRACT

Background. Patients on hemodialysis are at high-risk for complications derived from coronavirus disease 2019 (COVID-19). The present analysis evaluated the impact of a booster vaccine dose and breakthrough severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on humoral immunity 3 months after the booster dose.

Methods. This is a multicentric and prospective study assessing immunoglobulin G anti-Spike antibodies 6 and 9 months after initial SARS-CoV-2 vaccination in patients on hemodialysis that had also received a booster dose before the 6-month assessment (early booster) or between the 6- and 9-month assessments (late booster). The impact of breakthrough infections, type of vaccine, time from the booster and clinical variables were assessed.

Results. A total of 711 patients [67% male, median age (range) 67 (20–89) years] were included. Of these, 545 (77%) received an early booster and the rest a late booster. At 6 months, 64 (9%) patients had negative anti-Spike antibody titers (3% of early booster and 29% of late booster patients, \(P = .001\)). At 9 months, 91% of patients with 6-month negative response had seroconverted and there were no differences in residual prevalence of negative humoral response between early and late booster patients (0.9% vs 0.6%, \(P = .693\)). During follow-up, 35 patients (5%) developed breakthrough SARS-CoV-2 infection. Antibody titers at 9 months were independently associated with mRNA-1273 booster (\(P = .001\)), lower time from booster (\(P = .043\)) and past breakthrough SARS-CoV-2 infection (\(P < .001\)).

Conclusions. In hemodialysis patients, higher titers of anti-Spike antibodies at 9 months were associated with mRNA-1273 booster, lower time from booster and past breakthrough SARS-CoV-2 infection.

LAY SUMMARY

Patients on hemodialysis present higher rates of complications derived from SARS-CoV-2 infections. Initial vaccination schedules have demonstrated suboptimal responses in those patients. The aim of the present study is to evaluate the time-course of the humoral response after a booster dose of SARS-CoV-2 RNA-based vaccines (BNT162b2 or mRNA-1273) in patients on hemodialysis. We included 711 patients that had received a booster dose: 545 (77%) 6 months before the initial vaccination and 166 (23%) between 6 and 9 months from the initial vaccination. After the booster, only 6 (<1%) patients presented persistent negative humoral response. During follow-up from Month 6 to Month 9, 35 patients (5%) developed a SARS-CoV-2 infection. Patients that received the booster later, breakthrough SARS-CoV-2 infection and mRNA-1273 booster were associated with higher anti-Spike titers.
INTRODUCTION

Patients undergoing hemodialysis present higher mortality secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. SARS-CoV-2 vaccines attenuate the risk of complications such as severe coronavirus disease 2019 (COVID-19), hospitalizations or the need for intensive care admission [2]. However, the initial vaccination schedule against SARS-CoV-2 could be suboptimal in hemodialysis patients as anti-Spike antibodies decline over time [3]. Indeed, some reports have established the duration of anti-Spike antibodies in patients on hemodialysis between 4 and 6 months after vaccination, raising some concerns on the real effectivity of the initial vaccine schedule in this vulnerable population [4].

To avoid the clinical consequences of losing humoral immunity against SARS-CoV-2, many countries are offering a SARS-CoV-2 vaccine booster dose. The most widely prescribed booster is an mRNA vaccine (BNT162b2 or mRNA-1273). These mRNA vaccines enter many cell types but only some of them (i.e. immune cells) express the mRNA-encoded protein (Spike), which triggers the development of antibodies [5]. Although BNT162b2 and mRNA-1273 have similar mechanisms of action, the amount of mRNA differs (30 vs 100 μg, respectively). The development of anti-Spike antibodies seems to be lower in hemodialysis patients than in other cohorts, so additional strategies are required for maintaining their protection against COVID-19 [6].

A booster dose may protect from both spontaneous loss of anti-Spike antibodies and from new virus variants, such as Omicron, especially in immunosuppressed patients [7]. Recent small studies have shown that a booster dose in patients on hemodialysis helps in seroconverting patients with previous negative humoral responses [8, 9]. However, evidence is not strong enough to establish the ideal timing for prescribing a booster dose of SARS-CoV-2 vaccines in hemodialysis. In addition, the impact of breakthrough infections on humoral immunity has not been determined.

In the current study, we evaluated the time-course of the humoral response after a booster dose of SARS-CoV-2 RNA-based vaccines among patients on hemodialysis. In addition, we also determined the impact of breakthrough SARS-CoV-2 infections on anti-Spike antibody development.

MATERIALS AND METHODS

Study design

SENCOVAC is a multicentric study promoted by the Spanish Society of Nephrology. All patients in the present analysis had chronic kidney disease (CKD) on hemodialysis and had received both an initial SARS-CoV-2 vaccination schedule and a booster dose, following the local health authority’s guidelines. Prescribed initial vaccines were BNT162b2 (Pfizer-BioNTech®), mRNA-1273 (Moderna®), ChAdOx1-S (AstraZeneca®) or Ad26.COV.2 (Janssen®). In contrast, the booster was an mRNA-based vaccine [BNT162b2 (Pfizer-BioNTech®) or mRNA-1273 (Moderna®)] for all patients. The original protocol included
prespecified assessment of vaccine response at 3, 6 and 12 months and a 9-month assessment was later added as an amendment. In Spain, local authorities determined the type and timing of vaccines, stratifying by age and comorbidities. Hemodialysis patients were the second group that received the initial schedule (only after the elderly) and most of them were prescribed mRNA-based vaccines as they were the only available at that moment. For booster dosing in Spain, all patients received mRNA-based vaccine between 3 and 6 months after completing the initial schedule. The type of vaccine was determined by the local healthcare center, depending on availability of the different vaccines. Patients did not have the opportunity to choose the type of vaccine. Since this was an observational study and booster doses were recommended by health authorities after the study had been initiated, independently from the study investigators, the analysis of the impact of booster doses may be considered a post hoc analysis of prospectively drawn samples at prespecified 6- and 9-month timepoints.

Population

This is a pre-specified analysis that included all hemodialysis patients with anti-Spike antibody assessment 6 and 9 months after completing the initial vaccination schedule. Exclusion criteria were the lack of anti-Spike antibody assessment, solid organ transplantation, active oncological or hematological disease, primary immunodeficiency, human immunodeficiency virus and immunosuppressive treatment 6 months prior to vaccination [3, 10, 11]. Due to the different timelines of different regions and hospitals throughout Spain, some patients received the booster dose before the 6-month assessment (early booster) of anti-Spike antibodies and others between the 6- and 9-month assessments (late booster). This situation allowed division of the sample in two groups based on the timing of the booster, in a real-world pragmatic approach for evaluating the humoral response to the booster. Investigators did not intervene when determining the timing of the third dose, which fully depended on local health authorities.

Outcomes

The primary outcome was to evaluate the impact of a booster dose on humoral immunity, defined by anti-Spike immunoglobulin G (IgG) antibodies. Secondary outcomes included assessing anti-Spike IgG antibody development after breakthrough infections and exploring differences between RNA-based vaccines.

Variables and outcomes

At baseline, epidemiological variables and comorbidities were registered. CKD etiology, vascular access, dialysis modality and hemodialysis adequacy parameters were collected. Previous COVID-19 was defined as an infection before initial vaccination confirmed by any of the available techniques [real-time polymerase chain reaction (rt-PCR), antigen test or antibodies against SARS-CoV-2]. Humoral immunity was assessed 6 and 9 months after initial vaccination with blood samples that were sent to a central laboratory for testing by a CE-marked quantitative Virclia® IgG Monotest, Vircell SL, Spain), with a sensitivity and specificity of 96% and 100%, respectively, which detects IgG antibodies against the SARS-CoV-2 Spike protein. This assay was calibrated against the First WHO International Standard for anti-SARS-CoV-2 human immunoglobulin (NIBSC code: 20/136) and results were expressed as IU/mL. According to performance studies by the manufacturer, titers ≤32 IU/mL were considered negative, between 32 and 36 equivocal and >36 IU/mL positive, reflecting the presence of anti-Spike IgG antibodies resulting from previous infection or vaccination.

Breakthrough infections during follow-up

SARS-CoV-2 infections were registered during follow-up from 6 to 9 months. A positive rt-PCR or antigen test were required for confirming the SARS-CoV-2 infection.

Ethical concerns

The study was approved in February 2021 by the Ethical Committee (code SENCOVAC, ER_EO020-21_FJD-HRJC-HGV-HIE).

Statistical methods

Data are expressed as median (interquartile range). Categorical variables were compared using Fisher test and continuous variables with Mann–Whitney U test. Continuous variables from more than two groups were compared with the Kruskal–Wallis test. Logistic regression analysis was used to evaluate factors associated with humoral response after the booster dose. Multivariate logistic regression models adjusted for variables with \( P < .1 \) in univariate analysis and confounders were constructed. SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistics and GraphPad Prism version 9.02 (GraphPad Holdings, LLC) for plotting.

RESULTS

Baseline characteristics

Among the initial 2153 patients enrolled in SENCOVAC, 711 (33%) were included in the present analysis as they had anti-Spike antibody data for both the pre-specified timepoints of 6 and 9 months: 67% male, median age (range) 67 (20–89) years (Table 1, Fig. 1). The initial vaccination schedule was mainly based on RNA-based vaccines [233 (33%) BNT162b2, 471 (66%) mRNA-1273, 4 (1%) ChAdOx1-S and 3 (1%) Ad26.COV2]. Before the 6-month assessment, 545 (77%) patients had received a booster dose in contrast to 166 (23%) that received the booster between Months 6 and 9. In 230 (32%) patients, the booster dose was BNT162b2 and in 481 (68%) mRNA-1273 (Fig. 1).

Kinetics of anti-Spike antibodies after the booster dose

Amongst patients that received the booster before the 6-month assessment, anti-Spike titers at 6 months were significantly higher than in patients without booster by 6 months (\( P < .001 \)); however, they significantly decreased from 6 to 9 months [3788 (985–10 000) UI/mL vs 2807 (985–10 000) UI/mL] (\( P = .001 \)). In contrast, in patients who received the booster dose between the 6- and 9-month assessments, anti-Spike antibodies significantly increased from 6 to 9 months [142 (29–1666) UI/mL vs 6021 (1405–10 000) UI/mL] (\( P < .001 \)) (Fig. 2). As shown in Supplementary data, Fig. S1, patients that received an mRNA-1273 booster before the 6-month assessment developed higher titers of anti-Spike antibodies at 9 months than those receiving BNT162b2 before the 6-month assessment [3776 (1156–10 000) UI/mL vs 1712 (676–8423) UI/mL] (\( P < .001 \)). In contrast, in patients who received the booster from 6 to 9 months there were no significant differences.
in antibody titers at 9 months between types of RNA-based vaccines (P = .142), although the same trend was observed.

**Impact of breakthrough SARS-CoV-2 infection on anti-Spike antibodies**

During follow-up from Month 6 to Month 9, 35 patients (5%) developed a SARS-CoV-2 infection: 22/545 (4.0%) in the early booster and 13/166 (7.8%) in the later booster cohort (P = .063). Baseline characteristics of infected and non-infected patients are shown in Supplementary data, Table S1. At the 9-month assessment, patients with an infection during follow-up had higher titers of anti-Spike antibodies than those in the early booster cohort (10000 [4178–10 000] UI/mL vs 2665 [959–10 000] UI/mL) (P = .003) and in the late booster cohorts (10000 [8014–10 000] UI/mL vs 4443 [1365–10 000] UI/mL) (P = .021) (Supplementary data, Fig. S2).

**Anti-Spike antibody seroconversion**

Six months after the initial vaccine, 64 (9%) patients presented a negative humoral response, i.e. anti-Spike antibodies were not detected. Most had not yet received the booster dose (48/166, 29% in the later booster cohort vs 16/545, 3% in the early booster group) (P < .001) (Fig. 3). Beyond the booster, factors associated to higher anti-Spike titers at 9 months (Table 2). An adjusted linear regression showed that less time from booster to assessment (B = –0.12, P = .043) and mRNA-1273 booster (B = .17, P = .001) were independently associated to higher anti-Spike titers at 9 months (Table 2).

**Factors associated to higher anti-Spike titers**

Factors associated with higher anti-Spike titers at 9 months in univariate analysis were younger age (P = .025), late booster group, i.e. booster closer to antibody assessment (P = .030), less time from booster to antibody assessment (P = .004), breakthrough SARS-CoV-2 infection (P < .001) and mRNA-1273 booster (P = .001) (Table 2). An adjusted linear regression showed that less time from booster to assessment (B = –0.12, P = .043), breakthrough SARS-CoV-2 infection (B = 0.29, P < .001) and mRNA-1273 booster (B = 1.17, P = .001) were independently associated to higher anti-Spike titers at 9 months (Table 2).

**DISCUSSION**

The key finding of the present study is that persistent stimulation of the immune system, such as vaccine boosters and breakthrough infections, contributed to stronger antibody responses when compared with isolated stimulation, namely single or double vaccine dose, especially if the additional stimuli were recent. In addition, the controversial issue of humoral response duration and the impact of an early or late booster was addressed. Our data show that 6 months after initial vaccination, 29% of hemodialysis patients lacked IgG anti-Spike antibodies. However, most patients seroconverted after the booster dose. Indeed, only one patient lacked anti-Spike antibodies after the booster. As anti-Spike antibodies have been related to the severity of COVID-19 and monoclonal anti-Spike antibodies are used to treat COVID-19, it seems realistic to use the humoral response as a biomarker to stratify the risk of vulnerable patients.

Breakthrough infections enhance antibody development. In accordance with previous reports, our results showed that even in patients having received only the initial vaccination,
Third dose of SARS-CoV-2 vaccines in hemodialysis

Infections increased anti-Spike antibody titers to at least the same level as the booster dose at 6 months [13]. Indeed, previous reports from the SENCOVAC study showed that previous COVID-19 (even asymptomatic) was associated with higher humoral responses [3, 8]. As many SARS-CoV-2 infections remain asymptomatic, especially in vaccinated individuals, the only method available to assess anti-SARS-CoV-2 immunity would be to monitor anti-Spike antibodies to avoid hyperstimulation of immune cells by repeated boosters [14].

The type of vaccine is also a key driver for anti-Spike antibody development. As previously demonstrated for the initial vaccination schedule, patients that received the mRNA-1273 booster achieved stronger humoral responses [8]. This finding agrees with a prior study that compared two different types of a booster and supports that dose is directly related to antibody titer development, at least in hemodialysis patients, as mRNA-1273 contains approximately 3-fold more mRNA than BNT162b2 [15]. The choice of mRNA vaccine should be of especial interest in vulnerable patients with a rapid decline in pre-existing antibodies to optimize their antibody response [3, 8]. To our knowledge, non-mRNA vaccines, such as AZD1222 or Ad26.COV2.S, have not been used to booster hemodialysis patients. Their use in initial vaccination schedules resulted in lower antibody titers than mRNA-based vaccines [16, 17]. Importantly, a recent study has shown that heterologous vaccination (initial schedule and booster) with AZD1222 and BNT162b2 was insufficient to generate antibodies against Omicron [7]. Anecdotally, one small report has shown that a fourth vaccine dose is safe and increases anti-Spike antibodies in dialysis patients [18].
TABLE 2. Linear regression for factors associated to anti-Spike titers (per 103 UI/mL)

|                        | Univariate | Multivariate | P     | P     |
|------------------------|------------|--------------|-------|-------|
|                        | B (95% CI) | B (95% CI)   |       |       |
| Age (per year)         | -0.03       | -0.12        | 0.025 | 0.043 |
| Gender (male)          | 0.33        | 2.29         | 0.302 | <0.001|
| Late booster (yes)     | 1.08 (0.37, 1.78) | 1.17 (0.45, 1.89) | 0.030 | 0.001 |
| Time from booster (per week) | -0.21 (-0.19, -0.04) | -0.12 (-0.23, -0.01) | 0.004 | 0.043 |
| SARS-CoV-2 infection during follow-up (yes) | 3.01 (1.68, 4.28) | 2.29 (1.46, 4.39) | <0.001 | <0.001|
| Type of booster (mRNA-1273) | 1.05 (0.41, 1.68) | 1.17 (0.45, 1.89) | 0.001 | 0.001 |

* Linear regression adjusted for age, gender and date of booster.

Our study presents some limitations. First, breakthrough infections may have been underestimated, as asymptomatic SARS-CoV-2 infections may be unnoticed (i.e. local protocol for detecting SARS-CoV-2 infections differed and ranged from periodic screening of the hemodialysis population to testing only symptomatic individuals or contacts) and false-negative results may occur in PCR and antigen tests. However, severe SARS-CoV-2 infections increase anti-Spike titers to higher levels than asymptomatic infections, and the registered cases of our study were mostly symptomatic [19]. Second, for logistic reasons we do not have data on cellular immunity. This is a multicentric national study with more than 50 participating centers that presents serious challenges to the centralization of samples for this purpose. Beyond this, humoral immunity is probably the best choice for assessing protection against COVID-19 as it is easily measurable and affordable in routine clinical practice. Finally, observational studies have inherent biases. However, SENCOVAC was designed to be a prospective real-world study using a pragmatic approach.

In conclusion, breakthrough SARS-CoV-2 infections, time elapsed from booster dosing and type of booster are associated with higher anti-Spike titers in hemodialysis patients. Assessing the humoral response could be useful to stratify the need for close monitoring of SARS-CoV-2 infection, maintaining isolation measures and social distance, or the use of further booster doses.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

B.Q. has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme and Otsuka. M.J.S. is the CKJ Editor-in-Chief and reports honorarium for conferences, consulting fees and advisory boards from AstraZeneca, NovoNordsik, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, ICU Medical and Boehringer. A.O. is the former CKJ Editor-in-Chief and has received consultancy or speaker fees or travel support from Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Otsuka and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes. C.J.J.M. has received honoraria for one conference from
The present project has been supported by Fresenius Medical Care, Diaverum, Vifor Pharma, Vircell, Fundación Renal Iñigo Álvarez de Toledo and ISCIII FEDER funds RICORS2040 (RD21/0005). We thank all the involved centers and healthcare workers, especially the nurse team, for their involvement in this project. In addition, we want to thank the support of the Sociedad Española de Enfermería Nefrológica (SEDEN), Organización Nacional de Trasplantes (ONT) and Sociedad Española de Trasplante (SET). We also thank Ethical Committee of Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz which approved the study.

The SENCOVAC collaborative network:
Marta Puerta Carretero, Daniel Gaitán Tocora, Mª Teresa Jaldo Rodríguez, Tamar Talavá Anzón, Esther Rodríguez Suárez, Alfredo José Sáenz Santolaya, Raquel Cerrajero Calero, Patricia Arribas Cobo, Patricia Muñoz Ramos, Carolina Gracia-Iguacel, Catalina Martin-Cleary, Jinny Sánchez-Rodríguez, Ana Ramos-Verde, Yohana Gil Giraldo, Pablo Ruano Suárez, Antonio Fernández Perpén, Andrés Fernández Ramos, Laura Salanova Villanueva, Alejandra Cortiñas, Pablo A. Diez Arias, Alicia Cabrera Cárdenas, Antonio de Santos, Almudena Núñez, Guillermina Barril Cuadrado, Raquel Repollet, Francesc Moreso, María Antonieta Azancot, Natalia Ramos, Oriol Bestard, Ignacio Cidraque, Sheila Bermejo, Irene Agraz, Oretto Prat, Carlota Medina, Emma Pardo, Alejandro Saiz, Nicolás Menéndez Granados, María Jesús Corton Cabo, Walter López Alarcón, Simona Alexandru, Laura García Puente Suarez, Saul Pampa Saico, Marisol Poma Tapia, Laura Rodríguez Osorio, Rocío Zamora, Paloma Leticia Martin Moreno, Noelia Ania González, Ana Sabalza Ortiz, María Nieves Bastida Iñarrea, Teresa García, Carlos Narváez, Cristianh Orellana, José Luis Pizarro León, Manuel Antonio Martínez García, Benaldina García Jiménez, Juan de Dios Ramiro Moya, Diana López Espinosa, Alejandro Jiménez Herrador, Manuel Navarro Zurita, Leonardo Díaz Álvarez, Álvaro González Martínez, Sandra Baez Arroyo, Raquel Reina Fernández, Marilyn Janella Suárez Vargas, Rocío Calarano Casero, Gustavo Useche, Carmen Santamaría de Miguel, Ángel Palacios, Brenda Henningmeyer, Esther Otero Calvé, José Lacueva Moya, Sandra Castellano Gash, Lara Ruiz Martínez, Virginia Lopez De La Manzanara Perez, Marta Calvo Arevalo, Jose Antonio Herrera Calvo, Mercedes Salgueira, Nuria Areíst, María de los Ángeles Rodríguez, Rocio Collantes, Ana Isabel Martínez, María Jesús Moyano, Elena Jiménez Víbora, Aurelio Pastor Rodriguez Hernández, María Sagrario García Rebollo, Juana Margarita Rufino Hernández, Esther Torres Aguilera, Rolando Tello Alea, Margie Soledad Del Rosario Saldaña, Ana Maria Urraca de la Pisa, Lidia Sendino Monzon, Karina Ampuero Anachuri, Esther Hernández Garcia, Victoria Ovieido Gomez, Ignacio Manzur Cavalotti, Itziar Navarro Zorita, Sol Otero López, Sara Outon González, Carlos Soto Montañez, Manuel Ramírez de Arellano Serna, Luis Guirado Perich, Eva Cotilla de la Rosa.

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