

# Effectiveness of Recommendations to Prevent Reactivation of Latent Tuberculosis Infection in Patients Treated With Tumor Necrosis Factor Antagonists

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**Objective.** To investigate the impact of official recommendations regarding the management of latent tuberculosis (TB) infection on the rate of active TB in patients receiving treatment with tumor necrosis factor (TNF) antagonists.

**Methods.** Data on active TB rates and on screening and treatment of latent TB infection were extracted from the BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products), a registry of patients with rheumatic conditions treated with TNF antagonists. The rates of active TB among the BIOBADASER patients were compared with those in the background Spanish population, and BIOBADASER patients with rheumatoid arthritis (RA) were compared with a cohort of RA patients from the EMECAR (Morbidity and Clinical Expression of Rheumatoid Arthritis) study who were not treated with TNF antagonists and were followed up for 5 years.

**Results.** Active TB developed in 34 patients, of whom 32 started taking TNF antagonists prior to the official recommendations on latent TB infection (pre-OR) and 2 began treatment after the recommendations were issued (post-OR). All cases of TB occurred during treatment with infliximab, and 28 of these patients had RA. Pre-OR, the active TB rate in BIOBADASER patients was 20.9-fold higher than in the background Spanish population, while RA patients in the BIOBADASER had rates 22.6- and 6.2-fold higher than the background and EMECAR populations, respectively. Post-OR, 324 patients with a tuberculin skin test result  $\geq 5$  mm and/or chest radiograph findings suggestive of past TB were treated for 9 months with isoniazid (INH). Post-OR, active TB rates among the BIOBADASER patients decreased by 78% (incidence risk ratio [IRR] 0.22, 95% confidence interval [95% CI] 0.03–0.88;  $P = 0.008$ ), while among RA patients in the BIOBADASER, the rate dropped by 83% and reached the EMECAR rate (IRR 1.0, 95% CI 0.02–8.2). There were no INH treatment-related hospitalizations or deaths.

**Conclusion.** Strategies to treat latent TB infection that are tailored to the at-risk population can effectively and safely lessen the likelihood of active TB in patients treated with TNF antagonists.

Active tuberculosis (TB) that, in most instances, is the result of reactivation of latent TB infection has been associated with treatment with tumor necrosis factor (TNF) antagonists in patients with rheumatoid arthritis (RA) and Crohn's disease (1–5). Different recommendations for targeting patients with latent TB infection have been proposed worldwide by scientific organizations, health authorities, and other experts to decrease the risk of active TB (1,2,5–7), but, to date, the

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effectiveness of these recommendations has yet to be confirmed.

In February 2000, the Spanish Society of Rheumatology (SER) launched a registry (the Database on Biologic Products, or BIOBADASER; see Appendix A) that records data on patients with rheumatic conditions who are being treated with TNF antagonists. The primary objective of this database is to monitor the safety of such treatment. Over the past 4 years, more than 4,000 patients from 95 hospitals have been included in the registry and are followed up regularly (8).

An extremely high rate of active TB was detected in the first 2 years of this program, and these observations have been reported previously (2). Having been made aware of the problem, authorities from the Spanish National Health Service, in collaboration with the SER, advocated a set of recommendations in March 2002 for the management of latent TB infection in those patients receiving TNF antagonists (2) (details available at the SER Web site at [http://www.ser.es/archivosdescargables/infliximab\\_riesgo.pdf](http://www.ser.es/archivosdescargables/infliximab_riesgo.pdf)). It is recommended that patients in any of the following categories should be treated for 9 months with isoniazid (INH): 1) history of untreated or partially treated TB, or exposure to an active case of TB; 2) chest radiograph showing residual changes indicative of prior TB infection; and 3) reaction of  $\geq 5$  mm in diameter on the purified protein derivative of tuberculin skin test (TST) or on the 2-step TST procedure with an interval of 7–10 days between steps (2). Based on the information from the BIOBADASER, we provide, in this present report, an account of the effectiveness of these recommendations in a Spanish population of patients with rheumatic conditions who are at high risk of active TB.

## PATIENTS AND METHODS

A description of the BIOBADASER has been published previously (2). In brief, the BIOBADASER is a database that was established in February 2000 for the purpose of actively following up the long-term safety of biologic response-modifiers in patients with rheumatic diseases. The registry, which is supported by the SER and funded partially by the Spanish Medicines Agency, notes relevant adverse events that occur during treatment.

All hospital and community-based rheumatology units in Spain were invited to participate in setting up the project. The SER has a policy of maximum dissemination of information to all Spanish rheumatologists. Patients registered in the BIOBADASER are those with rheumatic diseases being treated with any of the currently approved biologic response-modifiers, as well as those who were treated before the database was created but for whom retrospective data are

available. The earliest records date back to January 1999. Patients treated with infliximab, etanercept, and adalimumab have been entered into the database. Data analyzed in the present study span the time period from the start of the registry up until April 2004. Infliximab was made available for clinical use in August 1999, etanercept in April 2003, and adalimumab in February 2004. The guidelines of the SER do not propose different criteria for prescribing any of the TNF inhibitors.

To guarantee confidentiality, the BIOBADASER does not include data that can possibly identify individual patients. Every patient has a lifetime alpha-numeric code randomly assigned among the participating centers. The database is physically located at the SER headquarters, where access is restricted and controlled by the scientific steering committee (a detailed description of the database is available at the Web site <http://biobadaser.ser.es/>).

Up until March 2002, the data were collected by participating physicians and information was recorded on standard forms, which were then faxed or sent by electronic mail to the SER headquarters. Since then, data have been reported by an electronic system. The following data are collected systematically: 1) identification of center, department, or unit, including contact person details; 2) data on patients, including sex, date of birth, diagnosis, and date of diagnosis; and 3) data on treatment, including type of treatment, start and discontinuation dates, and reason for treatment discontinuation, if applicable. Commencing on March 1, 2002, results from the TST and findings on the chest radiograph, as well as type of TB therapy, have been registered.

The quality of our database is ensured by a clear definition of its aim, an optimized number of variables, and an easy method of data collection that allows for checks on consistency (see the above-mentioned BIOBADASER Web site). Completeness and agreement of data with patients' charts were assessed on site by an audit of 15% of patient's records between December 2003 and March 2004. The audit indicated 21% incompleteness of relevant data (absence of communication of treatment discontinuation or of a relevant adverse event, and absence of information regarding date of diagnosis, TST results, and chest radiograph findings in TB cases), and complete agreement was observed in 100% of the data when the patient's record was directly compared with that contained in the BIOBADASER. All errors were accordingly corrected in our database. Thus, we expect that ~18% of the data reported herein are incomplete. Minor errors not affecting our analyses, such as errors in the date of diagnosis, date of chest radiograph, or data regarding the input center, were also found in ~40% of the data, and these were corrected accordingly.

For the purpose of the present study, a patient was classified as having active TB when *Mycobacterium tuberculosis* was isolated in any biologic specimen from an individual patient, in conjunction with an appropriate clinical picture. When necessary, physicians who reported a TB case were asked to provide information regarding the clinical presentation of the patient, results of the TST, health status according to the chest radiograph prior to commencing therapy, previous treatment of latent TB infection, and concomitant medications at the time of active TB infection. National TB rates (in 2001, 25 cases per 100,000 residents of Spain) were communicated

**Table 1.** Characteristics of the 2,833 rheumatoid arthritis patients treated with tumor necrosis factor (TNF) antagonists in the BIOBADASER registry\*

	Pre-OR	Post-OR
No. of patients	1,690	1,143
Women, %	78	78
Age, mean $\pm$ SD years	54 $\pm$ 13	50 $\pm$ 15
Disease duration, mean $\pm$ SD years	11 $\pm$ 8	10 $\pm$ 8
TNF antagonist, no. (%) <sup>†</sup>		
Infliximab	1,648 (87.6)	579 (46.7)
Etanercept	233 (12.4)	506 (40.8)
Adalimumab	0 (0)	154 (12.5)

\* The pre-OR (prior to official recommendations to prevent reactivation of latent tuberculosis infection) time period is defined as before March 2002, while post-OR (after official recommendations) is on or after March 1, 2002. BIOBADASER = Spanish Society of Rheumatology Database on Biologic Products.

<sup>†</sup> Some of the patients (n = 394) were treated with more than one TNF antagonist.

directly from the Committee on Tuberculosis and Respiratory Infections of the Spanish Society of Pneumology and Chest Surgery. The number of TB cases was confirmed in 2 ways: 1) by on-site monitoring, and 2) by contrasting our data with the Division of Pharmacoepidemiology (Med Watch system) of the Spanish Medicines Agency. According to the available information, there were no TB cases in the participating hospitals other than those reported to the BIOBADASER.

TB rates in patients with RA who have not been treated with TNF antagonists were obtained from the EMECAR (Morbidity and Clinical Expression of Rheumatoid Arthritis) study, comprising a cohort study funded by the SER. The EMECAR cohort was assembled in 1999 by random sampling from the clinical databases of 34 established rheumatology units (9,10) and is currently in its fifth year of followup. The sample includes 788 patients with RA from whom data on clinical presentation, activity of the disease, progression of the disease, and comorbidities are prospectively collected. EME-

CAR patients are representative of the RA population of Spain and cover the whole spectrum of disease severity.

The incidence rate of TB (per 100,000 patient-years) and 95% confidence intervals (95% CIs) were calculated. For the analysis, incidence rates were divided into the rate of active TB prior to the official recommendations issuance date of March 1, 2002, at which time recommendations were disseminated among physicians, and the rate on or after March 1, 2002 in patients treated with TNF antagonists, and these were compared with the rates in the background Spanish population and in the EMECAR cohort.

## RESULTS

A total of 2,729 female and 1,373 male patients, with a mean  $\pm$  SD age of 50  $\pm$  15 years, were registered in the BIOBADASER between January 2000 and April 2004. Of the registered patients, 69% have a diagnosis of RA (Table 1), 10% have ankylosing spondylitis, 10% have psoriatic arthritis, 4% have juvenile idiopathic arthritis, and the remaining 7% have a variety of other chronic inflammatory rheumatic conditions. There were 394 patients treated with more than one TNF antagonist, and 1,578 of the treatments commenced after March 1, 2002. The total treatment exposure rate was 7,825 patient-years (Table 2), and this was higher for infliximab (6,328 patient-years) than for etanercept (1,375 patient-years) or for adalimumab (122 patient-years). In RA patients the rate of exposure to TNF antagonists was 5,829 patient-years (Table 2), and was 1,996 patient-years in non-RA patients.

Data on the TST and chest radiography were recorded for 1,275 patients in the BIOBADASER after the official recommendations were issued. Complete or partial information is available on 84.9% of the patients.

**Table 2.** Rate of active TB in the BIOBADASER cohort before and after the specific recommendations, and risk ratio for the incidence of active TB compared with the risk in the background Spanish population and in the EMECAR patients\*

	Patient-years of exposure to TNF antagonists	No. of active TB cases	Active TB rate per 100,000 (95% CI)	IRR versus background (95% CI)	IRR versus EMECAR (95% CI) <sup>†</sup>
All TB cases					
Pre-OR	6,126	32	522 (369–738)	20.9 (12.0–36.8)	–
Post-OR	1,699	2	117 (29–470)	4.7 (0.5–18.9)	–
IRR <sub>recommendations</sub> <sup>‡</sup>	–	–	0.22 (0.03–0.88)	–	–
TB cases with RA only					
Pre-OR	4,780	27	564 (387–823)	22.6 (12.6–40.6)	6.2 (2.6–16.9)
Post-OR	1,049	1	95 (13–676)	3.8 (0.1–23.3)	1.0 (0.02–8.2)
IRR <sub>recommendations</sub> <sup>‡</sup>	–	–	0.17 (0.004–1.02)	–	–

\* TB = tuberculosis; IRR = incidence risk ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

<sup>†</sup> EMECAR patients were patients with rheumatoid arthritis (RA) who were not treated with TNF antagonists and were followed up for 5 years in the Morbidity and Clinical Expression of Rheumatoid Arthritis study.

<sup>‡</sup> IRR<sub>recommendations</sub> = incidence risk ratio comparing the rates of active TB before (pre-OR) and following (post-OR) the official recommendations implemented on March 1, 2002 for the management of latent TB infection.

An induration of  $\geq 5$  mm on the TST was reported in 359 patients (28%), and chest radiography findings suggestive of past TB were available for an additional 25 patients. According to the recommendations in place, 324 of 384 patients (84%) considered to have possible latent TB were treated with INH following March 1, 2002. There were no differences regarding sex, age, or diagnosis between patients with a possible latent TB infection who were treated with INH and those who were not treated with INH.

Active TB developed in 34 infliximab-treated patients, of whom 28 had RA. Thirty-two of these patients had started taking TNF antagonists before March 2002, and 2 began treatment subsequent to this date. Of the latter, 1 of the patients, who had RA, had a TST result  $\geq 5$  mm and was not treated with INH. The other patient was a 27-year-old man with ankylosing spondylitis, a normal chest radiograph, and a followup TST finding of 9 mm; he was treated with rifampicine and pyrazinamide (having lack of tolerance to INH) for 2 months, and after 1 month with this treatment, he was started on infliximab. Six months later he developed active TB. No cases of TB were reported among patients taking etanercept or adalimumab. Etanercept had been on the market for 1 year and adalimumab for only 3 months, and yet some patients had received these medications before as a compassionate treatment option.

The rate of active TB in patients starting TNF antagonists before March 1, 2002 was 20.9-fold higher than in the background population (Table 2). Among the RA patients in the BIOBADASER in this period, the rate was 22.6- and 6.2-fold higher than in the background population and the EMECAR patients, respectively. Conversely, following March 1, 2002, the active TB rate in the BIOBADASER cohort (Table 2) decreased by 78% (incidence risk ratio [IRR] compared with previous rate 0.22, 95% CI 0.03–0.88;  $P = 0.008$ ). Among RA patients in the BIOBADASER during the same period of time, the rate of active TB dropped by 83% (IRR compared with previous rate 0.17, 95% CI 0.004–1.02;  $P = 0.016$ ) and reached the rate observed among the EMECAR patients (IRR 1.0, 95% CI 0.02–8.2).

In infliximab-treated RA patients in the BIOBADASER, the risk ratio for the incidence of active TB, compared with the background population, before March 2002 was 25.15 (95% CI 14.05–45.17) and dropped 74% to 6.72 (95% CI 0.16–41.07) following the official recommendations date. The rate of TB in these patients after issuance of the official recommendations

reached the rate in the EMECAR population (IRR 1.85, 95% CI 0.04–14.40).

Abnormally high levels of aminotransferase (aspartate aminotransferase or serum glutamic pyruvic transaminase) were reported to be present in 25 patients (22 receiving infliximab and 3 receiving etanercept) in the BIOBADASER. Patients with elevated aminotransferase levels were not older than the remaining patients. Seven of the 25 patients (28%) were taking INH and 14 (56%) were taking methotrexate. None of the patients with high aminotransferase levels died or required hospitalization as a consequence of hepatic failure. There were 6 patients (24%) who discontinued therapy with TNF inhibitors and 1 patient with active TB who died of liver failure while being treated with INH and rifampicine.

## DISCUSSION

In the present study we investigated the impact of the SER recommendations in preventing reactivation of latent TB infection in patients receiving TNF antagonists, based on the number of active TB cases. Our study substantiates the effectiveness of this strategy, which includes a potential benefit from 9 months of INH therapy in patients with a TST result  $\geq 5$  mm and/or chest radiography finding suggestive of previous TB.

Among individuals who are exposed to *Mycobacterium tuberculosis*, 5% develop the disease and ~95% will harbor the organism, with 5% of the latter having a subsequent reactivation of the infection (5,11). The miscellaneous nature of the condition depends, in part, on a host response in which TNF and other cytokines have significant roles (12). The majority of cases of active TB occurring in patients receiving TNF antagonists are hypothesized to result from reactivation of latent TB infection. In the US, the estimated rate of active TB in RA patients who have received infliximab within the previous year is 24.4 cases per 100,000, and the rate of treatment exposure is 52.5 per 100,000 patient-years among those patients followed up prospectively (1,5). Both of these rates are much lower than the estimated rate in Europe (173 per 100,000) in the first year of therapy, and lower than the rate in the followup data reported in the present study. Of note is that, in the US, the rate of active TB in RA seems to be within the range of that in the background population (3).

Reports from other sources that have described active TB in RA have shown that the condition is usually related to treatments that could potentially favor infection. In conflict with these data is that a significantly

increased rate of active TB in RA patients who have not been treated with TNF antagonists has been reported in Spain (9). A pertinent difference is the incidence rate of active TB in the background population: 6.4 per 100,000 in the US compared with 25 per 100,000 in Spain. In this setting, it would be statistically easier to demonstrate a significant change with a smaller population in Spain than that in the US. Nevertheless, comparison of our findings with the rates of active TB in the background population and in a population of RA patients not treated with TNF antagonists (both sources with a similar setting) appears appropriate and relevant to our objectives. In the prospective EMECAR study, patients who developed TB after the diagnosis of RA did not have more severe disease than the patients who did not develop active TB. Moreover, the use of glucocorticoids or immunosuppressive drugs, and other risk factors, such as smoking, male sex, age, or chronic obstructive lung disease, were evenly distributed in patients with or without TB.

The substantial number of TB cases in our population and the active followup of patients treated with TNF antagonists have enabled us to confirm the effectiveness of the strategy devised to prevent reactivation of a latent TB infection, in a relatively small population of patients. There were 2 cases that occurred when the recommendations for the treatment of latent TB infection had been followed. This is not very surprising, since present evidence indicates that 9 months of treatment with INH does not fully protect against the development of active TB, although the decrease in the rate is ~70% (11,13), which is in concordance with our present findings. It is worth noting that 1 of these 2 patients did not complete 9 months of INH therapy because of intolerance; instead he was treated with rifampicine and pyrazinamide. Moreover, the second patient with a TST result  $\geq 5$  mm was not treated. In addition, the completion rate for 9 months of INH therapy in RA patients treated with TNF antagonists is not known with any accuracy, but it is likely to be low (14–16). Nevertheless, the impact of the recommendations may have been mitigated not only by the effects of prophylactic treatment, but also by the fact that physicians had been dissuaded from prescribing TNF inhibitors to patients who are regarded as being at high risk for TB.

The recommendation that a finding of  $\geq 5$  mm on the TST should be an indication for treatment with INH was established because of the high TB risk detected in this population in our area (13). In populations in which background TB rates are lower, other strategies have been proposed (4–6), including more stringent criteria

regarding TST results (for example, a cutoff of  $>9$  mm) prior to initiating treatment with INH. Whether the proposals would be as effective as the ones presented here would need to be explored. Nonetheless, our results ought not be extrapolated indiscriminately to other situations, since TB rates are governed by many factors. Furthermore, the benefit of INH should be balanced against the risk of developing toxicity-related hepatitis, which increases with age and can affect 10% of the treated patients (13,17). In our population, none of the patients treated with INH developed serious toxicity in the liver, but it remains a threat that should be considered, especially in the event of concomitant use of hepatotoxic drugs (18) other than INH or methotrexate. In addition, elevations in aminotransferase levels have been reported in patients treated with TNF inhibitors.

Of note is the absence of active TB in patients treated with etanercept or adalimumab. This requires cautious interpretation because it may pertain to the fact that fewer patients were taking etanercept as compared with infliximab before the screening tests were initiated, and etanercept was not commercially available. This disparity in usage before screening began could explain the differences in TB rate among patients taking various TNF antagonists. Nevertheless, the rate of TB has been reported to be increased among patients treated with all of the existing TNF antagonists, and our results could therefore reflect a real effect. Continuous reassessment of the risk of TB in this group and a consequent updating of the recommendations may be necessary.

It is almost axiomatic that voluntary medical registries contain several flaws. To be reliable, data must be of high quality (19). We have described the quality assurance of our database. The on-site audit of data uncovered 18% incompleteness, which is predictable in a voluntary event-based registry but still somewhat higher than the 0–17% previously reported (19). The 100% agreement of relevant data in the BIOBADASER with data from the patients' records is similar to that reported by others (20).

A major weakness of any recommendations made by officials or scientific organizations is that of implementation. In a number of cases registered in the BIOBADASER after March 1, 2002, the information regarding screening for latent TB was missing. This was despite the repeated and intensive dissemination of the recommendations. Taking into account the 18% incompleteness in the registry, we estimate that, in ~15% of patients, no effort was made to exclude the diagnosis of latent TB. An easily identifiable explanation for this shortcoming has yet to be found, but we believe that the

increased work-load borne by the attending physician and other members of the staff in the course of clinical management with these new therapies may be contributing to the problem and, as such, should be kept in mind in formulating future guidelines.

In summary, active TB is a serious possibility in patients treated with TNF antagonists. However, implementing strategies to deal with latent infection, tailored to the at-risk population, could lessen the likelihood of TB in a safe and effective manner.

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## APPENDIX A. PARTICIPATING INVESTIGATORS IN THE SPANISH BIOBADASER REGISTRY

The following investigators are participants in the BIOBADASER: Sara Marsal, Cristina Arnal Guimera (Ciudad Sanitaria Vall D'hebron); Laura Cebrián Méndez (Hospital Gregorio Marañón); Blanca Hernandez, Jose V. Montes de Oca Mercader, Federico Navarro Sarabia, Francisco Javier Toyos Saenz De Miera (Hospital Universitario Virgen Macarena); Isabel García Bernal, Antonio Mera Varela (Hospital Clinico Universitario de Santiago); Gema Bonilla Hernan (Hospital La Paz); Paloma Vela Casasempere (Hospital General Universitario de Alicante); Olga Maiz, Estibaliz Barastay (Hospital de Donostia-Edif. Guipuzcoa); Isidoro González Álvaro, Rosario Garcia de Vicuña Pinedo, Ana Maria Ortiz Garcia (Hospital Universitario de La Princesa); Sagrario Sanchez Andrada (Hospital Universitario Marques de Valdecilla); Oscar Illera Martin, Antonio C. Zea Mendoza, Paloma García de la Peña Lefebvre, Marta Valero Exposito (Hospital Ramon y Cajal); Enrique Judez Navarro (Hospital Clinico Universitario San Carlos); Tomas Tinture Eguren, Eduardo Loza Cortina (Hospital de Navarra); Francisco Javier Manero Ruiz, Eugenio Giménez Ruiz (Hospital Universitario Miguel Servet); Raimon Sanmartí Sala, Jose Ramón Rodríguez Cros, Juan D. Cañete (Hospital Clinic I Provincial); Carlos Rodriguez Lozano, Félix Francisco Hernández, Iñigo Rua Figueroa Fernandez (Hospital de Gran Canaria Dr. Negrin); Maria Victoria Irigoyen Oyarzabal, Inmaculada Ureña Garnica, Virginia Coret Cagigal (Hospital General Carlos Haya); Jose Roman Ivorra, Inmaculada Chalmeta (Hospital Universitario Dr. Peset); Ana Cruz Valenciano, Manuel Crespo Echeverria, Felix Cabero Del Pozo (Hospital Severo Ochoa); Carlos Marras Fernandez-Cid, Luis Francisco Linares Ferran, Juan Moreno Morales (Hospital Virgen De La Arrixaca); Rosa Roselló Pardo, Carlos Vazquez Galeano (Hospital General San Jorge); Mónica Fernández Castro, Carlos Isasi Zaragoza, Jose Luis Andreu Sanchez (Clinica Puerta De Hierro); Juan Carlos Vesga Carasa, Eduardo Cuende Quintana (Hospital Txagorritxu); Carmen Idalgo Tenorio (Hospital Virgen de Las Nieves); Maria Angeles Matias de La Mano, Isabel Mateo Bernardo, Patricia Carreira Delgado, Rosa González Crespo (Hospital 12 De Octubre); Carmen García Gómez, Oriol Codina, Jose Valverde García (Hospital de Bellvitge Princeps D'España); Jose Antonio Piqueras, Manuel Fernandez Prada, Javier Vidal Fuentes (Hospital General Universitario de Guadalajara); Joan Maymo Guarch, Carolina Pérez García (Imas. Hosp. de L'Esperança y Hospital del Mar); Javier Calvo Catalá, Cristina Campos (Hospital General Universitario de Valencia); Isabel Ibero Diaz, Vega Jovani Casado, Raquel Martin Domenech (Hospital General de Elda); Trinidad Pérez Sandoval (Hospital Virgen Blanca); Jose Raul Noguera Pons, Francisco J. Navarro Blasco, Juan Victor Tovar Beltran (Hospital General Universitario de Elche); Eduardo Rejón (Hospital Universitario de Valme); Ramon Mazzucchelli, Javier Quiros Donate, Pedro Zarco Montejo (Hospital Fundacion Alcorcon); Manuel Rodrí-

guez Gómez (Complejo Hospitalario De Ourense); Eduardo Collantes Estevez, Maria Carmen Castro Villegas (Hospital Universitario Reina Sofia); Juan Carlos Cobeta García (Hospital General de Teruel Obispo Polanco); Santiago Benito Urbina, J. A. López Martín, Jose Angel Cabezas Lefler (Complejo Hospitalario San Millan-San Pedro); Marta Larrosa Padro, Jordi Gratacos Masmijtja, Enrique Casado (Consorti Hospitalari Del Parc Tauli); Maria Teresa Ruiz Jimeno, Jaime Calvo Alen (Hospital Comarcal Sierrallana); Ivan Ferraz Amaro, Tomas Gonzalez Garcia, Alberto Alvarez Pio (Hospital Universitario de Canarias); Jesus Ibañez Ruan (Policlinico Vigo, S. A. [Povisa]); Juan Jose Garcia Borrás, Inmaculada Calvo (Hospital La Fe); Elena Ciruelo Monge, Eva Tomero Muriel, Olga Amengual (Hospital General De Segovia); Elena Cuesta (Hospital Virgen de La Luz); Amalia Sánchez-Andrade Fernández (Hospital Xeral-Calde); Encarnacion Saiz Cuenca, Jose Galvez Muñoz (Hospital General Morales Meseguer); Montserrat Centellas (Hospital de Mataró); Jordi Fiter Aresté, Luis Espadaler Poch (Hospital Son Dureta); Manel Pujol Busquets, Josep Granados Duran (Hospital Mutua Terrassa); Maria Teresa Bosque Peralta (Hospital Clínico Universitario Lozano Blesa); Lucia Pantoja Zarza, Maria Valvanera Pinillos Aransay (Hospital del Bierzo); Julia Garcia Consuegra, Rosa Merino Muñoz (Hospital Infantil La Paz); Javier Rivera Redondo, Teresa González Hernández (Instituto Provincial de Rehabilitacion); Vera Ortiz Santamaría (Hospital Universitari Germans Trias I Pujol); Alfredo Buisan Aguirre, Carlos Pascual Martín-Gamero (Hospital Militar Universitario Gomez Ulla); Carmen Torres, Montserrat Corteguera Coro (Hospital Nuestra Señora de Sonsoles); Javier Alegre López, Bonifacio Álvarez Lario, José Luis Alonso Valdivielso, Julia Fernández Melón (Hospital General Yagüe); Jose Luis Cuadra, F. Javier Paulino Tevar, Marcos Paulino Huertas (Hospital Nuestra Señora del Carmen); Xavier Arasa Fava (Hospital de Tortosa); Jordi del Blanco Barnusell (Hospital Sant Jaume de Calella); Anna Martinez Cristobal, Pilar Trenor (Hospital

de La Ribera); Inmaculada Bañegil (Hospital de Mendaro); Angel Aragón Díez (Hospital Nuestra Señora del Prado); Angel Garcia Aparicio (Hospital Virgen de La Salud); Emilia Aznar, Ricardo Gutierrez (Hospital Reina Sofia); Maria Francisca Pina Perez (Hospital Rafael Mendez); Miquel Angel Belmonte Serrano, Juan Beltran Fabregat, Juan Jose Lerma (Hospital General de Castellon); Jose Manuel Rodríguez Heredia, Angel Gallegos Cid, Jesús Garcia Arroba Muñoz, Miguel Cantalejo Moreira (Hospital Universitario de Getafe); Alberto Alonso Ruiz, Esther Uriarte Itzazelaia (Hospital de Cruces); Mauricio Minguez Vega, Gaspar Panadero Tendo (Hospital San Juan de Alicante); Miguel Angel Abad Hernandez, Maria Torresano Andres (Hospital Virgen del Puerto); Francisco Perez Torres (Hospital General de Requena); Ana Urruticoechea Arana (Hospital Can Misses de Ibiza); Dolors Boquet Estruch (Hospital Arnau de Vilanova); Jose Ivorra Cortes (Hospital General de Onteniente y Lluís Alcanyis de Xàtiva); Antonio Juan Mas, Inmaculada Ros Vilamajó (Fundación Hospital Son Llätzer); Cristina Medrano Le Quement (Hospital Internacional Medimar); Alfonso Corrales Martinez (Hospital Comarcal de Laredo); Jenaro Graña Gil (Hospital Santa Teresa); Saul Mario Gelman Aizen (Hospital General de Manresa); Eugenio Chamizo Carmona (Hospital General de Merida); Gaspar Pérez Lidon, Manuel Tenorio Martín (Hospital del Insalud Ceuta); Jose Carlos Rosas Gomez de Salazar, Gregorio Santos Soler (Hospital del S. V. S. de Villajoyosa); Cristina Hidalgo Calleja (Hospital de La Santísima Trinidad); Jaime Fernandez Campillo, Rocio Gonzalez Molina (Hospital del S. V. S. Vega Baja); Victor Eliseo Quevedo Vila (Hospital Comarcal de Monforte); Juan Pablo Valdazo De Diego (Hospital General Virgen de La Concha); Isabel Rotes Mas (Hospital de San Rafael); Roser Tuneu Valls (Centre Hospitalari Manresa); Gerardo Iglesias De La Torre (Hospital General Rio Carrion); Josep Pujol (Hospital de Sant Pau I Santa Tecla).