Risk factor assessment and counselling for 12 months reduces metabolic and cardiovascular risk in overweight or obese patients with schizophrenia spectrum disorders: The CRESSOB study

Background. Metabolic syndrome (MS) and cardiovascular risk factors (CRF) have been associated with patients with schizophrenia. The main objective is to assess the evolution of CRF and prevalence of MS for 12 months in a cohort of overweight patients diagnosed with schizophrenia schizophreniform disorder or schizoaffective disorder in which the recommendations for the assessment and control of metabolic and cardiovascular risk were applied.

Methods. The Control of Metabolic and Cardiovascular Risk in Patients with Schizophrenia and Overweight (CRESSOB) study is a 12-month, observational, prospective, open-label, multicentre, naturalistic study including 109 community mental health clinics of Spain. The study included a total of 403 patients, of whom we could collect all variables related to CRF and MS in 366 patients. Of these 366 patients, 286 completed the follow-up, (baseline, months 3, 6 and 12) where they underwent a complete physical examination and a blood test (glucose, cholesterol and triglycerides), they were asked about their health-related habits (smoking, diet and exercise) and they were given a series of recommendations to prevent cardiovascular risk and MS.

Results. A total of 403 patients were included, 63% men, mean age (mean; (SD)) 40.5 (10.5) years. After 12 months, the study showed statistically significant decrease in weight (p<0.0001), waist circumference (p<0.0001), BMI (p<0.0001), blood glucose (p=0.0034), total cholesterol (p<0.0001), HDL cholesterol (p=0.02), LDL cholesterol (p=0.0023) and triglycerides (p=0.0005). There was a significant reduction in the percentage of smokers (p=0.0057) and in the risk of heart disease at 10 years (p=0.0353).

Conclusion. Overweight patients with schizophrenia who receive appropriate medical care, including CRF monitoring and control of health-related habits experience improvements with regard to most CRFs.

Key Words: Schizophrenia, Metabolic Syndrome, Overweight, Cardiovascular Disease

La evaluación de factores de riesgo y el asesoramiento durante 12 meses reduce el riesgo metabólico y cardiovascular en pacientes con trastornos del espectro esquizofrénico con sobrepeso u obesidad: Estudio CRESSOB

Introducción. Se ha asociado la presencia del síndrome metabólico (SM) y de factores de riesgo cardiovascular (FRC) a pacientes con esquizofrenia. El principal objetivo es evaluar la evolución de los FRC y la prevalencia del SM durante 12 meses en una cohorte de pacientes con sobrepeso diagnosticados de esquizofrenia esquizofreniforme o de trastorno esquizoaffectivo a la que se aplicaron las recomendaciones para la evaluación y control del riesgo cardiovascular.
Método. El estudio del control del riesgo metabólico y cardiovascular en pacientes con esquizofrenia y sobrepeso [Control of Metabolic and Cardiovascular Risk in Patients with Schizophrenia and Overweight (CRESSOB)] es un estudio de 12 meses, observacional, prospectivo, abierto, multicéntrico, naturalístico que incluye 109 centros de salud mental en España. El estudio incluyó un total de 403 pacientes, de los cuales se recopilaron todas las variables relacionadas con FRC y SM en 366 pacientes. De esos 366, 286 completaron el seguimiento, (basal, a los 3, 6 y 12 meses) en el que se llevaron a cabo un examen físico completo y una analítica de sangre (glucosa, colesterol y triglicéridos), se les preguntó sobre hábitos de salud (tabaco, dieta y ejercicio) y se les ofreció una serie de recomendaciones para prevenir el riesgo cardiovascular y el SM.

Resultados. Un total de 403 pacientes fueron incluidos en el estudio, 63% hombres, de mediana edad [media 40,5 años; DE: (10,5)]. Transcurridos 12 meses, el estudio mostró descensos estadísticamente significativos en el peso (p<0,0001), circunferencia de la cintura (p<0,0001), IMC (p<0,0001), glucosa en sangre (p=0,0034), colesterol total (p<0,0001), colesterol HDL (p=0,02), colesterol LDL (p=0,0023) y triglicéridos (p=0,0005). Hubo una reducción significativa en el porcentaje de fumadores (p=0,0057) y en el riesgo de enfermedad cardíaca a 10 años (p=0,0353).

Conclusión. Los pacientes con sobrepeso y esquizofrenia que reciben cuidado médico apropiado, incluyendo la monitorización de FRC y el control de los hábitos de salud, experimentan mejora en la mayoría de los FRC.

Palabras clave: Esquizofrenia, Síndrome Metabólico, Sobrepeso, Trastorno cardiovascular

INTRODUCTION

More than two thirds of schizophrenia patients, compared with approximately one-half in the general population, die of all cardiovascular mortality1. Patients with schizophrenia spectrum disorders often present cardiovascular risk factors (CRF) and metabolic syndrome (MS)2-5, in addition to an unhealthy lifestyle including smoking6-7, abuse of alcohol or caffeine6, lack of exercise8-9, and diets rich in fats and sugars and poor in fruits and vegetables10-11. This already elevated risk of cardiovascular disease is exacerbated by the increased use of some atypical antipsychotic agents, especially olanzapine and clozapine, which are associated with CRF and MS12-17. The consequence is that this psychiatric population has an increased cardiovascular mortality18 and consequently a shorter expectancy of life than the general population1. Although cross sectional studies have evaluated the prevalence of MS in patients with schizophrenia, data from longitudinal studies are limited.

In view of this evidence, some clinical guidelines have been published in the US19, Europe20 and Spain21,22, recommending the assessment and control of metabolic and cardiovascular risk in patients with schizophrenia. Experts suggest that a baseline screening and assessment of CRF should be performed with all patients with schizophrenia, informing them and their relatives about CRF and the need for their prevention20. In addition, behavioral interventions focusing on dietary and physical activity modifications in these patients may prevent future CRF (e.g. obesity)23-24. These types of non-pharmacological interventions which include counselling, behavioral modification techniques or psychoeducation are simpler and less costly than some cognitive-behavioural treatments and may have a similar effectiveness23.

We hypothesised that merely assessing and informing about CRF to schizophrenia spectrum disorders patients and their relatives, could be effective in controlling CRF. The main objective of this study was to analyse in schizophrenia spectrum disorders patients with overweight or obesity whether the frequency of CRF and the cardiovascular risk at 10 years, varies after CRF assessment and counselling on healthy lifestyle issues during a 12-month period. In addition, if there is a physical improvement, we aimed to study whether this physical improvement leads to a reduction in mental symptoms and disability and better overall performance.

METHODS

Sample

The Control of Metabolic and Cardiovascular Risk in Patients with Schizophrenia and Overweight study (CRESSOB study) is a 12-month, naturalistic and multicentre study including 109 community mental health clinics of all the Spanish territory. This study was conducted from June 2007 to June 2009. Each community mental health clinic recruited up to four consecutive patients with diagnosis of schizophrenia, schizophreniform disorder and schizoaffective disorder. All participants were assessed by means of the clinician version of the Structured Clinical Interview25, as determined by criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR)26. Only overweight patients or obese patients [defined as a body mass index (BMI)≥25 kg/m²] at the study entry were included. We excluded patients younger than 18, those suffering from mental retardation or severe cognitive impairment, and those involved in a clinical trial.

The study included a total of 403 patients, of whom we could collect all variables related to CRF and MS in 366
patients. Of these 366 patients, 286 completed the follow-up. The sample included at baseline was described in detail in a previous report.27

Assessment instruments and procedures

The study comprised the following visits: visit 1 (baseline: day 1), visit 2 (month 3), visit 3 (month 6) and visit 4 (final visit: 12 months). The schedule of visits and outcome research procedures performed at each visit are shown in Table 1. After the procedures had been fully explained, all patients gave written informed consent, following the protocol for patients approved by the Institutional Review Board of the University Clinic of Navarra. This research complied with the principles of the Declaration of Helsinki regarding medical research in humans.28

At the baseline interview, socio-demographic data (sex, age, marital status, number of siblings and children, years of formal education and occupational status) and clinical data (psychiatric and medical history, personal and family history of cardiovascular risk, substance abuse (tobacco, alcohol and illegal drugs), and lifestyle habits including diet and physical activity) were collected. In this first visit, a physical examination including measures of weight, height, waist circumference and blood pressure was carried out; and fasting blood samples were collected to determine levels of glucose, total cholesterol, High Density Lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides. In line with World Health Organization (WHO) criteria, Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and those overweight or obese patients (BMI≥25 kg/m²) were included in the study. Pharmacological treatment for the subjects was based on the clinicians’ choice. A combination of two or more antipsychotics was used in 58% of subjects; and the most frequently used antipsychotics in the subjects initially included in the study were ziprasidone, risperidone and olanzapine (49.8%, 37.3% and 24.2% of the sample). Subjects also received other pharmacologic treatments such as hypnotic/anxiolytic drugs prescribed to 43.9% of the subjects, antiepileptic drugs to 22.1% and antidepressant drugs to 20.0%. Anticholinergic medication for movement disorders were prescribed to 14.4%.

Cardiovascular risk was estimated using the Framingham function which is calculated from the values for age, gender, total cholesterol, HDL cholesterol, systolic arterial pressure, diabetes and smoking habit.30 This function is a mathematical probability model obtained using multivariate analysis techniques from follow-up studies of individuals in the general population, in which the incidence of a fatal or non-fatal coronary heart disease event (including besides any mortality due to cardiovascular disease) is estimated. The value of the Framingham function is expressed as a 10-year probability of an event or as a lifetime probability of an event.29

Table 1 Schedule of outcome research evaluation

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
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<tr>
<td>Selection criteria</td>
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<td>Sociodemographic data</td>
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<td>Personal and family antecedents of cardiovascular risk</td>
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<td></td>
</tr>
<tr>
<td>Physical examination (Blood pressure, weight, height, waist circumference)</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BMI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Metabolic variables (Glucose, cholesterol, triglycerides)</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular risk (Framingham, SCORE)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Lifestyle habits (diet and physical activity)</td>
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<td></td>
<td></td>
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<tr>
<td>PANSS</td>
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<td>X</td>
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<tr>
<td>Remission criteria (PANSS)</td>
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<tr>
<td>GAF</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment and changes</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; PANSS = Positive and Negative Symptoms Scale; GAF = Global Assessment of Functioning; EQ-SD = Euro Quality of Life-5 dimensions
Information about cardiovascular risk

In accordance with the recommendations of the European Psychiatric Association and other panel experts, we provided information to the patient and to the family at baseline and at each visit.

This information consisted of recommending the need for having an appropriate body weight and a healthy diet (eating more fruits and vegetables, fibre and fish, and less salt and fatty foods). The patients were also encouraged to stop smoking and reduce alcohol consumption to one drink per day, as well as to increase physical exercise. Finally, the patients were informed of the need for appropriate control of blood pressure, blood glucose and lipid profile, referring them to their general practitioners or specialists for treatment with antihypertensive or sugar-lowering agents or statins, if necessary.

All this advice was summarised in an explanatory leaflet that was given both to the patient and his/her relatives or primary caregiver.

Statistical analysis

Statistical analysis was performed using the SAS version 8.2 statistical package. Quantitative and qualitative variables were analysed using measurements of central tendency (mean, median) and of dispersion [95% confidence interval (CI)]. Qualitative variables were defined according to their absolute and relative frequencies. Dimensional variables and frequencies were compared by parametric or non-parametric tests, as appropriate. The individual prevalence of each cardiovascular risk factor (Framingham) and the prevalence of MS were estimated by the direct method, calculating the corresponding 95% confidence intervals. Changes from baseline to 12 month of clinical variables and CRF were examined using McNemar test and Student’s t-test for paired samples. Missing post-baseline information (due to early withdrawal or to visits that were missed) was extrapolated using the last observation carried forward (LOCF) algorithm. All statistical tests were 2-tailed and p<0.05 was considered statistically significant.

RESULTS

Socio-demographic characteristics of the sample at the baseline are summarised in Table 2. The proportion of males was 62% and participants’ mean age was 40.5 (95% CI=39.4-41.5) years.

As it is shown in Table 3, after 12-months, schizophrenia spectrum disorder patients who are overweight or obese receiving the appropriate counselling regarding healthy lifestyle habits and routine monitoring of CRF showed a significant decrease of anthropometric (weight, BMI and waist circumference) and analytic (blood glucose, total cholesterol, LDL cholesterol and triglycerides) parameters; and a significant increase of HDL cholesterol. In addition, the proportion of current smokers decreased significantly after the follow-up period (Table 3). From baseline to month 12 there was a significant increase of subjects who controlled saturated fat/cholesterol consumption (27% vs. 41.9%; p<0.001), or consumed a high fibre diet (40.3% vs. 45.3%; p=0.0181). Finally, the proportion of subjects who did not perform physical activity decreased significantly from baseline to month 12 (30% and 19% respectively; p<0.001).

According to the calibrated Framingham equation, there was a significant reduction of the risk of a coronary event at 10 years from baseline to month 12 (8.4; 95% CI=7.4-9.41 vs. 7.8; 95% CI=6.93-8.75; p=0.0353). The prevalence of MS decreased from 62.3% at baseline to 60.2% at 12 month, for both men and women, but this change was not statistically significant (p=0.695).

The psychotic symptoms improved significantly at the final visit compared with those seen at baseline in the total score of the PANSS (80.7 ±25.4 vs. 69.7 ±24.9; p <0.001) as well as the positive (17.4 ±7.4 vs. 14.3 ±6.2; p <0.001) and negative scores (23.3 ±8.2 vs. 20.1 ±7.8; p<0.001). In addition, the proportion of subjects who achieved symptomatic remission criteria (according to PANSS score) increased significantly from baseline to the end of the follow-up (22.5% and 49.2% respectively; p<0.001).
There was a statistically significant improvement in the GAF score at the end of the study (52.7±15.2 vs. 60.3±14.9; p<0.0001). The proportion of subjects who had a score of 60 or higher in the GAF was significantly higher from baseline to the end of the study (33% and 52.6% respectively; p<0.0001). The mean total score in EQ-5D increased significantly from baseline to month 12 (59.4±16.9 and 66.8±14.4 respectively; p <0.001).

DISCUSSION

In our study after 12-months follow up, subjects with schizophrenia spectrum disorders and with BMI≥25 who received the appropriate medical care, controlled lifestyle habits and routinely monitored CRF, had reductions in most of the modifiable cardiovascular and metabolic risk factors (body weight, waist circumference, BMI, blood glucose, lipid profile, and cigarette smoking) as well as reductions in the 10-year risk of coronary heart disease events. In addition, there was a significant improvement in psychiatric symptomatology, as well as in functioning and the health status. Patients also improved their dietary habits, with a healthier diet, and exercised more at the end of the study. Moreover, this physical improvement was associated with a reduction in mental symptoms (measured by PANSS scale) and in disability (measured by GAF and EQ-5D).
One of the strengths of this study is that it is a multicentre, naturalistic study conducted in typical patients found in regular clinical practice and that its duration was sufficient to see effects on the parameters to be assessed (12 months). The study was conducted in patients throughout Spain, so our findings can be extrapolated to countries with similar characteristics. The study shows that, when analysing a sample of high risk patients (overweight patients with schizophrenia spectrum disorders), we can easily reduce their CRFs merely by monitoring and assessing them.

The limitations include the fact that data about patients who left the follow-up are not available, and that the clinicians were unable to obtain all the study variables from all the patients. In our study 22% of the patients did not completed the study. The main reason for study discontinuation was lost of follow-up (82.5%), and the majority (55%) was seen during the first three months of the study. However this dropout rate is lower than expected in studies performed in patients with schizophrenia. The percentage of withdrawals in the CATIE study due to patients’ decision as well as other reasons do not related with lack of efficacy or tolerability was 35%42. Wahlbeck43 also pointed out that one-third of the subjects dropped out of the antipsychotic drug trials.

Although our analyses are only based on the data obtained, some of the results could be biased, probably in the sense that the differences obtained are slightly smaller, as patients who are lost to follow-up are usually those with worse physical and mental performance. Moreover, the fact that there was no control group prevented us from comparing MS and CRF prevalence figures. In this respect, our study does not have the statistical power of randomised clinical trials (see44 for a meta-analysis) and it is not possible to conclude that the monitoring and counseling had an effect on metabolic outcomes.

The prevalence of both MS (62.3%) and CRFs found is the highest encountered in a group of patients with schizophrenia, and much higher than that found in both international44,45 and Spanish studies46,47. This is probably because our study was conducted in high-risk patients, as all our subjects were overweight. With regard to 10-year coronary risk (Framingham), our results are similar to those found by McCreadie11 (10.5% in men and 7% in women) and somewhat higher than those presented by Bobes45 (8.3% in men and 4.5% in women) and Goff46 (9.4% in men and 6.3% in women). Our results are slightly higher for men and lower for women, so when including overweight patients there could be a greater impact on men.

<table>
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<tr>
<th>Variables</th>
<th>N</th>
<th>Baseline</th>
<th>Month 12</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>363</td>
<td>93.4 (17.9)</td>
<td>91.4 (18.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>363</td>
<td>32.8 (5.1)</td>
<td>32.1 (5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>296</td>
<td>113.0 (16.7)</td>
<td>110.7 (16.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood Glucose (mg/dl)</td>
<td>287</td>
<td>103.1 (26.5)</td>
<td>99.2 (21.0)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>289</td>
<td>219.9 (47.5)</td>
<td>211.5 (42.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>229</td>
<td>47.5 (17.1)</td>
<td>49.5 (16.2)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>217</td>
<td>139.7 (42.5)</td>
<td>132.9 (36.5)</td>
<td>&lt;0.0023</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>275</td>
<td>174.1 (91.4)</td>
<td>161.1 (77.6)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>322</td>
<td>78.8 (10.8)</td>
<td>79.2 (9.9)</td>
<td>&lt;0.395</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>375</td>
<td>196 (52.3)</td>
<td>188 (50.1)</td>
<td>&lt;0.0057</td>
</tr>
</tbody>
</table>

N = total number of subjects; SD = Standard Deviation; BMI = Body Mass Index; DBP = Diastolic Blood Pressure

*p value for change from baseline to month 12 was based on the McNemar test; p≤0.05 was considered statistically significant
Patients with schizophrenia spectrum disorders often present CRF such as obesity, type 2 diabetes mellitus, dyslipidaemia, hypertension and MS. Our most important finding is the reduction of all these CRFs (except hypertension) caused by MS. Although the reduction found in the prevalence of MS was not statistically significant, it could reach significance if this type of intervention were applied for a period longer than 12 months in contrast with other programmes with a longer duration (see for review).

The improvement in weight reduction that we have found is similar to that resulting from cognitive-behavioural and psycho-educational treatments (see for review). Nevertheless, our intervention is much simpler, does not involve extra training and can be applied by general medical staff (such as nurses). Moreover, our study is also more comprehensive because not only does it show a reduction in weight, like previous studies (see for meta-analysis), but it also finds an improvement in other CRFs.

The percentage of smokers in our sample was similar to that of prior studies. We found a statistically significant reduction of more than two points in this percentage. It has been documented that a reduction of 10% in cholesterol levels results in a 30% reduction in cardiovascular disease (CVD) risk, a decrease in blood pressure of 4% to 6% decreases CVD risk 15%, maintaining a BMI less than 25 lowers risk 35% to 55% and smokers with schizophrenia who stop smoking tobacco would benefit by a near 75% reduction in the likelihood of a 10-year cardiovascular event risk above 10%.

The improvement in CRFs, together with better dietary habits (healthier diet and more physical exercise) was associated in our sample with a reduction in mental symptoms (measured by PANSS), and better overall performance and quality of life (measured by GAF and
EuroQol). To our knowledge, this is the first non-interventional study that finds that schizophrenia spectrum disorders patients who participate in a cardiovascular and metabolic follow-up intervention not only improve both these aspects but also show relief of their disease’s symptoms. Recent studies said that MS aggravate injury of cognitive function in chronic schizophrenia; this type of association between physical and mental health had only previously been found in clinical trials, in which these aspects were improved by means of antipsychotic medication, not a non-interventionist programme.

Our study shows that a simple and inexpensive intervention would help to drastically reduce CRFs in a group of patients who, according to some studies, do not normally receive appropriate treatment for these conditions, either because they are not referred to specialists or because they show poor adherence to the prescribed treatments. These parameters are not often measured and controlled by the psychiatric community. Moreover, young patients are more sensitive to body image and self-esteem issues, thus transforming weight gain into social discrimination and stigma; this may exacerbate the natural pharmacological noncompliance that characterizes younger patients, less disposed to adhering to medication regimens.

FUNDING AND OTHER SUPPORT

This study was sponsored by Pfizer. Pfizer contributed to and approved the study design and the final draft of the manuscript. A CRO, European Biometrics Institute, was engaged by Pfizer to conduct the study, including logistics, monitoring, data management, and statistical analysis. Pfizer oversaw the entire process of the study.

CONFLICT OF INTEREST

Dr L. Gutiérrez-Rojas has been a spokesperson for and advisory board member of Bristol-Myers Squibb, Janssen-Cilag, Astra-Zeneca, Roche, Lundbeck, Lilly, Otsuka, GSK and Pfizer. Ms. S. Pulido and Mr. F.J. Mesa are employees of Pfizer. Prof. Dr J.R. Azanza has been a spokesperson for and advisory board member of Janssen-Cilag, Pfizer, Astra-Zeneca, GSK, Roche, Novartis, Recordati, Norgine, Gilead, Astellas, MSD and Sanofi. Prof. Dr M. Bernardo has been a spokesperson for and advisory board member of Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Mylan, Organon and Pfizer. Prof. Dr L. Rojo has been a spokesperson for and advisory board member of Janssen-Cilag and Pfizer. The rest of the authors have no transmitted any conflict of interest.

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