Tocilizumab in giant cell arteritis: differences between the GiACTA trial and a multicentre series of patients from the clinical practice

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ABSTRACT

Objective. *A potential point of concern among clinicians is whether results derived from the clinical trials can be reasonably applied or generalised to a definable group of patients seen in real world. It can be the case of the GiACTA study that is a phase III randomised controlled trial of tocilizumab (TCZ) in giant cell arteritis (GCA). To address this question, we compared the clinical features and the response to TCZ from the GiACTA trial patients with those from a series of GCA seen in the daily clinical practice.*

Methods. *Comparative study of clinical features between patients from the GiACTA trial (overall n=251) and those from a multicentre series of real-world GCA patients undergoing TCZ therapy (n=134). The diagnosis of GCA in the GiACTA trial was established by the ACR modified criteria whereas in the series of real-world patients it was made by using the ACR criteria, a positive biopsy of temporal artery or the presence of imaging techniques consistent with large-vessel vasculitis in individuals who presented cranial symptoms of GCA. GiACTA trial patients received subcutaneous TCZ (162 mg every 1 or 2 weeks) whereas those from the clinical practice series were treated using standard IV dose (8 mg/kg/month) or subcutaneously (162 mg/week).*

Results. *Real-life patients undergoing TCZ were older with longer disease duration and higher values of ESR and had received conventional immunosuppressive therapy (mainly methotrexate) more commonly than those included in the GiACTA trial. Despite clinical differences, TCZ was equally effective in both GiACTA trial and clinical practice patients. However, serious infections were more commonly observed in GCA patients recruited from the clinical practice.*

Conclusion. *Despite clinical differences with patients recruited in clinical trials, data from real-life patients confirm the efficacy of TCZ in GCA.*

Introduction

Giant cell arteritis (GCA) is the most common vasculitis in the elderly, involving medium- and large-sized blood vessels, that can lead to irreversible complications (1-3). The cornerstone of GCA treatment are glucocorticoids, which must be initiated immediately after diagnosis at high dose (2, 3). Nevertheless, glucocorticoids in ageing people frequently lead to side-effects and some patients are refractory to this therapy (2, 4-7). Other drugs such as methotrexate (MTX), leflunomide, azathioprine, hydroxychloroquine, cyclophosphamide or TNF-α inhibitors have been used with controversial or negative results (3, 8-14).

Tocilizumab (TCZ) was found to be effective in both the clinical practice (15-25) and two randomised clinical trials (RCTs) on GCA (26, 27). Results derived from the Giant-Cell Arteritis Actemra (GiACTA) trial is a phase III, a randomised, double-blind placebo-controlled trial, served for the approval

of this biologic therapy for the management of GCA. This trial showed that TCZ was able to yield a sustained glucocorticoid-free remission (27).

RCTs are considered the best tool to assess the efficacy of therapeutic agents (28). However, they are conducted under strict inclusion criteria and, therefore, they often exclude real-world patients and situations to make the statistical assessment of efficacy and/or safety more efficient. Therefore, inter-individual variability is usually reduced (29, 30) and effectiveness and safety can be altered (29, 31-33). More importantly, clinical features of patients included in RCTs may differ from real-world patients (34-38). This fact raises some concern on the applicability to RCTs to the daily clinical practice (39, 40).

Real-world evidence (RWE) is generated from analysing real-world data (RWD) obtained from clinical practice. These studies provide information of clinical decisions in usual clinical practice, data frequently not available in RCTs. It is also important to highlight that RWE reflects the treatments based on the clinical characteristics of the patients and on the preferences of the physicians and patients. RWD help to estimate specially the safety of the therapies, although the evaluation of effectiveness is more controversial (41). For this reason, it is very important to carry out observational studies to evaluate if RCTs estimate apply to a target population in real world (34, 35, 40-43).

Taking all these considerations into account and considering that a potential point of concern among clinicians is whether results derived from the clinical trials can be reasonably applied or generalised to a definable group of patients seen in real world, we compared the clinical features and the response to TCZ from the GiACTA trial patients with those from a series of GCA treated with TCZ who were seen in the daily clinical practice.

Patients and methods

Patients, enrolment criteria and study subgroups

We carried out a comparative study between our series of 134 patients with GCA treated with TCZ in a real scenario (17) and the patients of the GiACTA clinical trial (27).

The study was approved by the Clinical Research Ethic Committee.

The design of the real-world clinical study was previously described (17). Briefly, real-world patients were diagnosed with GCA at the Rheumatology or Autoimmune Units of 40 Spanish referral centres. GCA diagnosis in this series was based on a) American College of Rheumatology (ACR) criteria (44), b) positive biopsy of temporal artery (TAB) and/or c) presence of imaging techniques consistent with large-vessel vasculitis (LVV) in patients with cranial symptoms of GCA. The main imaging techniques used for the diagnosis of LVV was ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) scan, magnetic resonance imaging angiography (MRI-A), computed tomography angiography (CT-A), and helical CT scan. Treatment of GCA was based on the classic therapeutic management, starting with high doses of glucocorticoids, using conventional immunosuppressive drugs and biologic therapy in refractory or relapsing patients. In this regard, TCZ was prescribed at standard intravenous dose (8 mg/kg/4 weeks) or subcutaneously (162 mg/week). TCZ was given due to relapsing disease or because of lack of efficacy and/or unacceptable adverse side-effects related to previous therapies. In most cases, TCZ was prescribed off-label since it was indicated before its approval by the EMA and the FDA for GCA treatment. Therefore, a written informed consent was obtained in these cases.

The design and results of GiACTA trial were reported elsewhere (27, 45). This was a phase III, randomised, double-blind placebo-controlled trial which evaluated the effect of TCZ on the rates of relapse during glucocorticoid tapering in GCA patients. To be recruited in the GiACTA trial, the patients had to meet the following criteria: a) age ≥50 years; b) history of Erythrocyte Sedimentation Rate (ESR) ≥50 mm/1st hour or C-Reactive Protein (CRP) ≥2.45 mg/dL if ESR was unavailable; c) at least one of the following findings: 1) unequivocal cranial symptoms of GCA (new-onset localised headache, scalp or temporal artery tenderness, ischaemia-related vision loss, or otherwise unexplained mouth or jaw pain on mastication); 2) unequivocal symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory stiffness; and d) at least one of the following data: 1) TAB revealing features of GCA, 2) evidence of large-vessel vasculitis by angiography or imaging study such as MRI-A, CT-A or PET/CT.

For the purpose of the present study, we aimed to determine if there were clinical differences between patients from the GiACTA trial and those from a multicentre series of real-world Spanish GCA patients undergoing TCZ therapy. With respect to this, we established the following comparisons: comparative analysis of the clinical features of the whole series of 134 real-world GCA patients with those from the whole series of GiACTA trial patients (GiACTA overall; n=251) and with only GiACTA trial patients who experienced relapses (GiACTA only relapsing; n=132). In addition, further comparison of the clinical features between the subgroup of real-world Spanish patients who fulfilled the GiACTA trial criteria (n=43) and those from the GiACTA trial patients was performed.

Differences in definitions between the two cohorts of patients

In the real-world cohort, an *ESR* value greater than 20 mm/1st h in men or >25 mm/1st h in women was considered abnormal while *serum CRP* was considered to be increased when it was higher than 0.5 mg/dL. In GiACTA trial, *ESR* and *CRP* were considered elevated when their values were ≥30 mm/h and 1 mg/dL, respectively.

In the real-world clinical practice group, *remission* was defined as the absence of flares and the normalisation of the acute phase reactants (CRP and ESR) at the next study visit. *Prolonged remission* was defined by the absence of clinical symptoms and signs and normalisation of the acute phase reactants for at least 6 months. *Relapse* was defined as the recurrence of signs

or symptoms of GCA and/or ESR >20 mm/1st h in men or >25 mm/1st h in women, and/or serum CRP >0.5 mg/dL related to GCA, both before and after starting TCZ therapy.

In the GiACTA trial, *remission* was defined as the absence of flare and the normalisation of the CRP value (<1 mg/dL); *sustained remission* was defined as remission from week 12 through week 52 and adherence to the prednisone taper. *Flare of the disease* (the equivalent of *relapse* in the real-world cohort) was defined as the recurrence of signs or symptoms of GCA or as an elevation of ESR ≥30 mm/1st h attributable to GCA. In the GiACTA trial, a *serious adverse event* was considered to be present when a life-threatening event, fatal or requiring hospitalisation occurred, or when it led to persistent or significant disability. In our clinical practice series, we used the same definition, adding the use of intravenous antibiotics for the definition of *serious infection*.

Data collection

Information was retrieved from the results of the GiACTA trial (27, 46) and from our clinical practice GCA series (17).

Statistical analysis

For the comparative analysis described above, all the continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were reported in percentages. Comparisons between means were based on the 95% confidence interval (95% CI) for the difference of means based on a Student t distribution. Comparisons between proportions were based on 95% CI for the difference, and this difference was tested by the Z statistic. Statistical analyses were performed by using a free software from tabulated data, EPIDAT v. 3.1 (https://www.sergas.es).

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Results

Baseline clinical characteristics of patients at TCZ onset

The mean age of the patients of the clinical practice series was significantly higher than that of the patients of the GiACTA study, both in the whole series and in the group of patients with relapsing GCA.

Since 47.4% of the patients from the GiACTA trial were newly diagnosed GCA whereas all the real-life patients were initially treated with glucocorticoids, the mean time between the diagnosis of GCA and the onset of treatment with TCZ was significantly lower in the series of the GiACTA (p<0.0001).

The mean time between the diagnosis of GCA and the onset of treatment with TCZ was also significantly lower in the subgroup of relapsing patients from the GiACTA trial than in the real-world series (p=0.003).

The most common clinical manifestations reported before TCZ onset were cranial symptoms in both GiACTA trial and real-life GCA patients. They were present in 79.3% of the patients enrolled in GiACTA trial and in 55.2% of the clinical practice patients (p<0.0001). Interestingly, in both GiACTA trial and real-life cohort, PMR symptoms in the absence of cranial manifestations were observed in 20% of patients at the time of TCZ onset. However, a statistically significant difference between acute phase reactants was observed. In this regard, the mean ESR at TCZ onset was 24±19.4 mm/1st h in the GiACTA trial and 40.5±31.2 mm/1st hour in the clinical practice group (p<0.0001). Regarding the frequency of positive TAB, there were no significant differences between both groups. Nevertheless, imaging techniques were performed more commonly in the subgroup of real-life patients who fulfilled the GiACTA trial definitions than in the GiACTA trial group itself (p=0.012), being PET/CT the imaging technique most frequently performed.

Table I summarises the main baseline characteristics of all these groups of patients.

Treatment with TCZ and outcomes

At the time of TCZ onset all patients were on glucocorticoid therapy. However, the mean initial dose of glucocorticoids at the beginning of TCZ therapy was higher in patients from the GiACTA trial than in the real-life series (p<0.0001). Nevertheless, the percentage of patients who had received immunosuppressive agents prior to TCZ onset was higher in patients from the clinical practice cohort. MTX was the most commonly used. In this regard, 70.1% of patients from the clinical practice series had received MTX compared to 10.7% of those from the GiACTA trial. TCZ was given subcutaneously to all patients included in the GiACTA trial whereas it was administered intravenously to 79.1% of the clinical practice series. Despite these differences in the route of administration, the number of patients achieving sustained remission was almost similar in both groups (54.6% in the GiACTA trial *vs*. 70.4% in clinical practice group; p=0.42).

Data on safety of TCZ in both cohorts

Serious adverse events were observed throughout the follow-up period in 14.8% of the patients from the GiACTA group compared to 23.9% in the clinical practice series (p=0.7).

Infections were the most frequent adverse event reported in both cohorts. The most frequent infections reported in clinical practice series were pneumonia (n=3), urinary infection (n=2), facial herpes zoster infection (n=2), bacterial infective bursitis and cellulitis (n=2). The remaining infections are described in our previous study (17). Specific causes of infection were not specified in the GiACTA cohort.

TCZ had to be discontinued due to side effects in 6% of the patients from the GiACTA group and in 12.7% of the real-life patients (p=0.08) (Table III). There were not reported deaths in the GiACTA trial whereas they were reported in 5 patients from the real-life series.

Discussion

The present study indicates that real-life patients with GCA, who require TCZ therapy, are clinically different from the GCA patients included in the GiACTA trial, which was the pivotal study used for the approval of this

Table I. Baseline characteristics of patients in our series and those of GiACTA at TCZ onset.

	GiACTA (overall) (n=251)	GiACTA (only relapsing GCA) (n=132)	Clinical practice (overall) (n=134)	Clinical practice (with GiACTA criteria) (n=43)	GiACTA overall *vs*. clinical practice overall (*p*-value)	GiACTA relapsing *vs*. clinical practice overall (*p*-value)	GiACTA overall *vs*. clinical practice (GiACTA criteria) (*p*-value)
Women /Men, n (%)	188 (74.9) /63 (25.1)	99 (75) /33 (25)	101 (75.4) /33 (24.6)	37 (86) /6 (14)	0.98	0.94	0.16
Age (years), mean (SD) at TCZ onset	69 (8.2)	69.1 (8)	73 (8.8)	71 (8.5)	<0.0001	0.0002	0.14
Newly diagnosed GCA[&]/ refractory GCA, n (%)	119 (47.4)/132 (52.6)	0/132 (100)	0/134 (100)	0/43 (100)	<0.0001 / <0.0001	-	-
Months from GCA diagnosis up to TCZ onset, mean (SD)	9.1 (16.8)	16.9 (20.3)	27.5 (35.8)	22.8 (27.1)	<0.0001	0.003	0.002
Positive TAB, n (%)	156 (62.1)	82 (62.1)	72 (53.7)	31 (86.1)	0.14	0.21	0.28
Imaging techniques performed, n (%)	138 (55)	70 (53)	75 (56)	33 (76.7)	0.93	0.72	0.012
Positive imaging	119 (47.4)	59 (44.7)	58 (43.3)	32 (74.4)	0.51	0.91	0.002
Positive MRI-A, n (%)	8 (3.2)	4 (3)	16 (11.9)	2 (4.7)	0.002	0.01	0.97
Positive CT-A, n (%)	13 (5.2)	7 (5.3)	4 (3.0)	4 (9.3)	0.46	0.52	0.47
Positive PET/CT, n (%)	97 (38.7)	42 (31.8)	52 (38.8)	30 (69.8)	0.93	0.29	0.0003
ESR (mm/1st hour), mean (SD) at TCZ onset ESR mm/1st hour, mean (SD)	24 (19.4)	26.8 (19.6)	40.5 (31.2)	63.5 (27.8)	<0.0001	<0.0001	<0.0001
Manifestations at TCZ onset							
PMR (total), n (%)	166 (66.1)	-	73 (54)	32 (74.4)	0.003	-	0.37
Isolated features of PMR, n (%)	51 (20.3)	-	28 (20.9)	-	0.99	-	-
Other Signs/symptoms of GCA, n (%) [§]	199 (79.3)	-	74 (55.2)	30 (69.8)	<0.0001	-	0.23

[&]Diagnosis of GCA made within 6 weeks of baseline visit.
[§]Signs or symptoms of GCA include headache, scalp tenderness, jaw claudication, fever, constitutional syndrome.
CT-A: computed tomography angiography; ESR: erythrocyte sedimentation rate; GiACTA: giant-cell arteritis actemra; LVV: large-vessel vasculitis; MRI-A: magnetic resonance imaging angiography; PET: positron emission tomography; PET-CT: positron emission tomography-computed tomography; PMR: polymyalgia rheumatica; SD: standard deviation; TAB: temporal artery biopsy; TCZ: tocilizumab.

Table II. Treatment before TCZ onset and clinical response.

	GiACTA (overall) (n=251)	GiACTA (only relapsing) (n=132)	Clinical practice (overall) (n=134)	Clinical practice (with GiACTA criteria) (n=43)	GiACTA overall *vs*. clinical practice overall (*p*-value)	GiACTA relapsing *vs*. clinical practice overall (*p*-value)	GiACTA overall *vs*. clinical practice, (GiACTA criteria) (*p*-value)
Patients on corticosteroids at study onset, n (%)	251 (100)	132 (100)	134 (100)	43 (100)	-	-	-
Prednisone (mg/d) at TCZ onset, mean (SD)	40 (13.1)	30.2 (12)	21.7 (16.1)	20.6 (15)	<0.0001	<0.0001	<0.0001
Previous immunosuppressant agents, n (%)	27 (10.8)	23 (17)	98 (73.1)	32 (74.4)	<0.0001	<0.0001	<0.0001
- Methotrexate, n (%)	27 (10.7)	23 (17)	94 (70.1)	31 (72.1)	<0.0001	<0.0001	<0.0001
Previous biologic therapy, n (%)	–	–	3 (2.2)	1 (2.3)	-	-	-
TCZ route	SC	SC	IV (106) / SC (28)	IV (35) / SC (8)	-	-	-
Follow-up on TCZ therapy, months median [IQR]	12	12	12 [3-24]	12 [6-24]	-	-	-
Sustained remission, n (%)	82 (54.6)	–	50 (70.4)	18 (69.2)	0.42	-	0.32
Serious adverse events, n [100 patients/year]	[¥]27 [29.1] / [¬]10 [21.9]	--	32 [21.1]	9 [15.3]	[¥]0.32 / [¬]0.06	-	[¥]0.0002 / [¬]<0.0001
Serious infection, n [100 patients/year] [±]	[¥]9 [9.7] / [¬]2 [4.4]	–	16 [10.6]	5 [8.5]	[¥]0.13 / [¬]0.004	-	[¥]0.0001 / [¬]<0.0001
TCZ withdrawal, n (%)[¤]	9/149 (6)	--	17 (12.7)	5 (11.6)	0.08	-	0.36

±Serious infection was considered to be present when a life-threatening infection (fatal, or requiring hospitalisation) occurred, intravenous antibiotics were required or the infectious process led to persistent or significant disability.
[¤]because of adverse events. [¥]Patients who received TCZ weekly. [¬]Patients who received TCZ every other week.
GiACTA: giant-cell arteritis actemra; SD: standard deviation; TCZ: tocilizumab; IQR: interquartile range.

biologic agent for the management of patients with GCA (27). Nevertheless, despite clinical differences, data from real-world patients confirmed the efficacy of TCZ in GCA (15, 17).

Since in real-life patients TCZ is more commonly used in GCA patients who are refractory to glucocorticoids and/or conventional immunosuppressive agents, these patients often have longer disease duration prior to the onset of this biologic agent.

Isolated PMR manifestations were the reason for prescribing TCZ in 20% of GiACTA trial and real-life cohort. Since PMR and GCA are often overlapping conditions (47) and PMR may be the presenting manifestation of GCA (48-50), the efficacy of TCZ in GCA patients presenting predominant PMR manifestations support the opinion of

Table III. Adverse events that required tocilizumab withdrawal.

	Clinical practice (17/134)	GiACTA trial (9/149)
Infections	Type Non-specified	
Cytomegalovirus (bilateral pneumonia)	1 (4.8%)	
Endocarditis	1 (4.8%)*	
Infectious meningitis	1 (4.8%)	
Infected ulcer †	1 (4.8%)	
Infected necrotising ulcer	1 (4.8%)*	
Pneumonia	3 (14.3%)	
Urinary sepsis	1 (4.8%)	
Haematological alterations§		
Myelodysplastic syndrome	1 (4.8%)	
Neutropenia grade IV	1 (4.8%)	
Neutropenia grade III		6 (4%)
Neoplasia		
Colon adenocarcinoma	1 (4.8%)	
Lung cancer	1 (4.8%)*	
Cardiovascular		
Atrioventricular blockade	1 (4.8%)	
Hypertensive crisis	1 (4.8%)	
Others		
Alzheimer's disease	1 (4.8%)	
Liver toxicity#	1 (4.8%)	3 (2%)
Myopathy	1 (4.8%)	
Stroke	2 (9.5%)*	
Unexpected death	1 (4.8)*	

Six patients from the clinical practice series presented more than1 side-effect.
*Causes of death.
†Requiring hospitalisation and intravenous antibiotics.
§Neutropenia grade III was definedd if neutrophils 500-1000/mm3, and neutropenia grade IV if neutrophils < 500/mm^3.
#Grade 3 elevation of the ALT (alanine aminotransferase): 5 to 10 times the upper limit of normal.

experts on a potential beneficial effect of anti-IL-6 blockers in the management of refractory PMR (51-53). With respect to this, clinical studies indicate that this biologic therapy may be useful in patients with isolated PMR who are refractory to glucocorticoids (54).

Relapses are common in patients with GCA (6, 55). They were common in the cohort of real-life patients, being one of the main reasons for prescribing TCZ. Since relapses are often associated with increased of acute phase reactants, the higher values of ESR in the real-life cohort than in the GiACTA trial are somehow expected.

The older age and the longer disease duration observed in the real-life series, along with a greater cumulative dose of glucocorticoids, than in patients from the GiACTA trial, may explain that the frequency of infections was higher in the real-world Spanish series. In this regard, serious infections occurred in 6% of the patients from the GiACTA trial (27) whereas they were reported in 11.9% (10.6 per 100 patients-year) of the patients from the clinical practice series (17). Therefore, we recommend that before using TCZ in older patients, the increased risk of developing infections should be considered.

Our study has potential limitations derived from the observational and retrospective nature of the real-life cohort, making it very difficult for the definitions of relapse, remission and sustained remission to be the same in the GiACTA trial group as in the real-life cohort. Another limitation of this study was the difficulty in comparing the glucocorticoid-sparing effect of TCZ, since in our study (real-life cohort), being retrospective, the cumulative prednisone dose could not be calculated, although in our previous study TCZ proved to be effective to minimise glucocorticoid exposure over time (17).

In conclusion, the present study indicates that real-life patients with GCA undergoing TCZ therapy are clinically different from those of the GiACTA trial. It may be due to the most common use of this biologic agent in real-life patients who are refractory to glucocorticoids and conventional immunosuppressive agents. Nevertheless, it is possible that the clinical spectrum of real-life GCA patients undergoing anti-IL-6 receptor blockers may be different in the near future, if these biologic agents become more affordable in terms of price, and consequently used in earlier stages of the disease. As shown in the GiACTA trial, an earlier use of anti-IL-6 receptor therapy may reduce the cumulative glucocorticoid dose that, in turn, may lead to a decrease in the frequency of infections observed in these patients.

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Competing interests

M. Calderón-Goercke has attended conferences Lilly, Abbvie and Pfizer. V. Aldasoro had consultation fees/participation in company sponsored speaker's bureau from Janssen, BMS, MSD, Roche, Sanofi, Pfizer, Novartis, Amgen, Lilly, Abbvie, Gebro, Nordic, Lacer, Alter, UCB, ASAC Pharma, Menarini and Celgene. D. Prieto-Peña has attended conferences Lilly, Roche and Pfizer. E. Pérez-Pampín had consultation fees/participation in company sponsored speaker's bureau from MSD, BMS, Janssen, Abbvie, Novartis, Pfizer, Roche, UCB, Lilly, Celgene, Nordic. F. Sivera received grants from Roche. A. Olivé-Marqués had consultation fees/participation in company-sponsored speaker's bureau from Roche, MSD, Pfizer, Schering-Plough, Aventis, Lilly, GSK, Wyeth, Abbvie, BMS, Almirall, BMS, Sanofi. M. Álvarez del Buergo has attended conferences Abbvie, MSD, Actelion, and Pfizer. L. Marena-Rojas had consultation fees/participation in company sponsored speaker's bureau from Roche, Sandoz, Pfizer, Menarini, Janssen, Amgen and Gebro. E. Galíndez-Agirregoikoa had consultation fees/participation in company sponsored speaker's bureau from Celgene, Abbvie, Pfizer, Roche, Lilly, MSD, Janssen and Bristol. J. Loricera has attended conferences with Novartis, Abbvie, Roche, MSD, Bristol-Myers Squibb, Lilly, Pfizer and Celgene, and has participated in courses and lectures sponsored by Novartis, MSD, Abbvie, Celgene and Gebro Pharma. S. Manrique-Arija had consultation fees/participation in company sponsored speaker's bureau from Pfizer, Abbvie, MSD, UCB, Lilly, Novartis and Roche. P. Vela received grants/research supports from Abbvie, Pfizer, BMS, Novartis, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Pfizer, BMS, Lilly, UCB and MSD. E. De Miguel had consultation fees/participation in company sponsored speaker's bureau from Abbvie, Novartis, Pfizer, BMS, MSD, UCB, Roche, Grünenthal and Janssen. J.C. Nieto had consultation fees/participation in company sponsored speaker's bureau from MSD, Pfizer, BMS, Nordic, Pharma, Sanofi, Abbvie, UCB, Novartis, Gebro, Janssen, Lilly, Roche and Advisory Board from Sanofi, Lilly, Abbvie and MSD. N. Ortego had consultation fees/participation in company sponsored speaker's bureau from Actelion, Abbvie, Roche and Advisory Board from Roche and Boehringer. M. Corteguera had consultation fees/participation in company sponsored speaker's bureau from Amgen and MSD. M.A. Gonzalez-Gay received grants/research supports from Abbvie, MSD, Jansen and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Pfizer, Celgene, Novartis, Roche, MSD, Sanofi and Lilly. R. Blanco received grants/research supports from Abbvie, MSD and Roche, and had

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