Demyelinating Disease in Patients Treated with TNF Antagonists in Rheumatology: Data from BIOBADASER, a Pharmacovigilance Database, and a Systematic Review

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Objectives: To estimate the rate of demyelinating diseases in patients with rheumatic diseases treated with tumor necrosis factor (TNF) antagonists and to describe the cases reported to 3 different pharmacovigilance sources.

Methods: All confirmed cases of demyelinating disease, optic neuritis, and multiple sclerosis (MS) in patients with rheumatic diseases treated with TNF-antagonists were reviewed from 3 different sources: (1) the Spanish Registry of biological therapies in rheumatic diseases (BIOBADASER); (2) the Spanish Pharmacovigilance Database of Adverse Drug Reactions (FEDRA); and (3) a systematic review (PubMed, EMBASE, and the Cochrane Library). In BIOBADASER, the incidence rate per 1000 patients was estimated with a 95% confidence interval (95%CI).

Results: In 21,425 patient-years in BIOBADASER, there were 9 patients with confirmed demyelinating disease, 4 with optic neuritis, and 1 with MS. In addition, 22 patients presented polyneuropathies, paresthesias, dysesthesias, facial palsy, or vocal cord paralysis without confirmed demyelination. The incidence rate of demyelinating disease in patients with rheumatic diseases exposed to TNF antagonists in BIOBADASER was 0.65 per 1000 patient-years (95%CI: 0.39-1.1). The incidence of MS in BIOBADASER was 0.05 (95%CI: 0.01-0.33), while the incidence in the general Spanish population was 0.02 to 0.04 cases per 1000. Compared with BIOBADASER, cases in FEDRA ($n = 19$) and in the literature ($n = 48$) tend to be younger, have shorter exposure to TNF-antagonists, and recover after discontinuation of the drug.

Conclusions: It is not clear whether TNF antagonists increase the incidence of demyelinating diseases in patients with rheumatic diseases. Differences between cases depending on the pharmacovigilance source could be explained by selective reporting bias outside registries.

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The role of tumor necrosis factor-α (TNF-α) in the pathogenesis of inflammatory demyelinating disease of the central nervous system has been demonstrated in experimental autoimmune encephalomyelitis in rodents (1) and in humans (2-4). Plaques and cerebrospinal fluid of patients with multiple sclerosis (MS) have high concentrations of TNF-α (5,6), and in experimental autoimmune encephalomyelitis, the blockade of TNF-α with antibodies or soluble TNF-receptors decreases the severity of the disease (7). Unexpectedly, the literature shows reports of patients with inflammatory diseases who developed demyelinating lesions in the central and peripheral nervous system in plausible relation to treatment with TNF antagonists (8-10). The possible mechanisms underlying this suspected effect of TNF antagonists are unclear.

The rate of demyelinating disease in patients with immune-mediated chronic conditions treated with TNF antagonists is a matter of interest. It is particularly important to assess whether the demyelination rate is increased compared with the expected rate in the general population, or compared with patients suffering from other immune-mediated chronic conditions, as they occasionally appear in clusters (11-14).

Safety signals arise from several sources that may then be confirmed or not in cohort studies. Traditionally, alerts to rare or new adverse drug events have been triggered by spontaneous notification and case reports. However, the absence of a common denominator prevents real capture of a risk, which needs to be confirmed in adequately designed prospective studies. Biologics observation registries provide a unique opportunity to test safety signals from other sources (15).

The purpose of the present study was to estimate the incidence of demyelinating processes in patients with rheumatic diseases treated with TNF antagonists and to describe the characteristics of the cases obtained from different pharmacovigilance sources.

METHODS

The information presented herein was obtained from the following sources: (1) the Spanish Registry of adverse events of biological therapies in rheumatic diseases (BIOBADASER); (2) the Spanish Pharmacovigilance Database of Adverse Drug Reactions (FEDRA); and (3) a systematic literature review on demyelinating diseases reported as an adverse event of TNF antagonists.

The BIOBADASER Registry

A detailed description of BIOBADASER has been published elsewhere (16-18). In brief, BIOBADASER is a national registry established in February 2001 for active long-term follow-up of the safety of biological drugs in rheumatic patients. The BIOBADASER database unifies 100 participant centers and includes all rheumatic patients receiving biological therapies, regardless of the type of rheumatic disease. Only those receiving TNF antagonists were included in this study. BIOBADASER registers "relevant" adverse events according to the ICH E2E definition of "serious" (19). Data are reported online by participating physicians. New patients, treatment modifications, and adverse events are communicated at the time they occur. The following data are collected systematically: (1) patient data, including gender, date of birth, diagnosis, date of diagnosis, diagnosis specifications, and comorbidities; (2) data on the biological treatment: type, start, and discontinuation dates, reason for discontinuation, and concomitant treatments; and (3) data on adverse events according to the MedDRA dictionary (20), including date of occurrence, severity, and outcome. Once a year, consistency of data is validated by on-site audits. Additional validation is performed by contacting the patients annually to assess hospital admissions and vital status. BIOBADASER protocols and materials were approved by the Hospital Ramón y Cajal (Madrid) Ethics Committee, and patients gave their written informed consent to be contacted. Patients coming from centers where the audits revealed incompleteness of the data were censored at the time of the last reliable information.

Only cases described with the MedDRA-preferred terms "demyelination," "optical neuritis," and "multiple sclerosis" and documented by a physician in the clinical chart were considered in the study. Patients with symptoms associated with demyelination (eg, paresthesia) but without confirmation of demyelination were not included. A request for additional information was sent to the rheumatologists of the identified cases and cases with associated symptoms.

FEDRA Database

The FEDRA database registers spontaneous adverse drug reactions of approved drugs as reported to the Spanish Pharmacovigilance System since 1985. Health care professionals report directly to FEDRA using a yellow card or through marketing authorization holders. Terms used by the reporter are coded using the Medical Dictionary for Regulatory Activity (MedDRA version 11.1) (21). FEDRA was searched using the standardized MedDRA query (SMQ) "demyelination" and each of the available TNF-antagonists, in the period from 1985 to 16 January 2009. SMQ search group events that indicate the presence of a condition that typically presents itself through different preferred terms. Thus, the SMQ "demyelination" compiles terms related and less related to MS (including optic neuritis, polyneuropathy, etc).

Systematic Review

A systematic literature search of Medline (PubMed from 1996 to October 2008), Embase (from 1991 to October 2008), and the Cochrane Library combined 2 groups of terms: (demyelinating diseases, multiple sclerosis, and optic neuritis) AND (TNF antagonist, anti-TNF, TNF

Table 1 Description of Demyelinating Cases in BIOBADASER

Age/ Sex	Dx	Disease Duration (yr)	Anti-TNF						Adverse Event	Treatment	Outcome
			Previous	Current	Exposure (yr)	Stop[a]	GC	MTX			
67/F	RA	0.7		INF	3.63	No	Yes	Yes	DD	GBP, amitriptyline	Partially recovered
55/F	RA	16.9		INF	0.82	Yes			DD	GBP	Recovered
41/F	RA	1.6		INF	1.50	Yes	Yes	Yes	DD	GBP	Not recovered
50/F	RA	3.4		INF	0.54	Yes	Yes	Yes	DD	No treatment	Recovered
42/M	AS	1.7		ETA	0.35	Yes			DD	IVIG	Not recovered
26/M	AS	5.6		ETA	2.24	Yes			DD	GC, Interferon b	Not recovered
52/F	PsA	1.8		INF	0.27	Yes		Yes	DD	GC, IVIG, Mitroxantone.	Not recovered
55/F	RA	22.0		ADA	0.04	Yes			DD	No treatment	Not recovered
48/M	RA	7.4	INF	ETA	1.82	Yes		Yes	DD (GBS)	GBP	Recovered
67/F	RA	15.4		INF	1.10	Yes			MS	No treatment	Recovered
60/M	RA	0.2		ETA	0.23	Yes			ON	GC	Not recovered
56/M	PsA	4.6		INF	1.44	Yes			ON	Unknown	Unknown
48/F	RA	10.4	INF	ETA	2.03	Yes			ON	GC	Recovered
48/F	PsA	19.1		INF	4.12	Yes		Yes	ON	GBP	Not recovered

Dx, diagnosis; GC, glucocorticoids; MTX, methotrexate; M, male; F, female; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; MS, multiple sclerosis; ON, optic neuritis; DD, demyelinating disease; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin; GBP, gabapentin.
[a]TNF-antagonist was discontinued.

blocker, tumor necrosis factor-alpha/administration and dosage, tumor necrosis factor-alpha/adverse effects, tumor necrosis factor-alpha/drug effects, tumor necrosis factor/therapeutic, tumor necrosis factor-alpha/toxicity, infliximab, remicade, enbrel, etanercept, humira, and adalimumab). The selection criteria were as follows: (1) to include any reference to a demyelinating adverse event in patients suffering from rheumatic diseases treated with TNF antagonists; and (2) to refer to rheumatic diseases, based on their long-term treatment exposure as opposed to the shorter treatment in psoriasis or Crohn's disease. No limits regarding study design were imposed and the search included any clinical trial, observational study, and case reports or series. The search was restricted to English and Spanish publications. The identified records were then selected by title and abstract by 2 independent reviewers for detailed review. References with an uncertain title and without an available abstract were included in this review. Additionally, a manual search of the references from the selected articles not identified in the previous search was performed.

Analyses and Presentation of Data

Data from FEDRA and the systematic review are presented as described in the original source. The incidence rate per 1000 patient-years was estimated with a 95% confidence interval (CI) in BIOBADASER. The following criteria were taken into account in the estimations: (1) only patients treated with TNF-antagonists were included; (2) only patients with any rheumatic diagnosis were included; (3) exposure was considered from the initiation of the corresponding TNF-antagonist until twice the half-life after discontinuation, death, loss to follow-up, or censor date, whichever occurred first. All patients and treatments from February 2001 until September 2008 were included. All data analyses were performed using Stata 10.0 (Stata Corp., College Station, TX, 2008).

RESULTS

Cases of Demyelinating Diseases in the BIOBADASER Registry

Up to 1 September 2008, BIOBADASER contained information on 9256 patients receiving anti-TNF therapies, with a total exposure of 21,425 patient-years. Exposure of patients with rheumatoid arthritis (RA) was 13,075 patient-years, with ankylosing spondylitis (AS) 2870 patient-years, and with psoriatic arthritis (PsA) 2873 patient-years. Nine patients had a confirmed demyelinating disease—of which 1 was a case of Guillain Barre's syndrome and the others were unspecified lesions—4 had optic neuritis, and 1 fulfilled MS criteria (Tables 1 and 2). In addition to these cases, there were 22 patients with 1 or more symptoms potentially associated with demyelination, such as polyneuropathy ($n = 12$), paresthesia ($n = 6$), dysesthesia ($n = 2$), facial paralysis ($n = 5$), or vocal cord paralysis ($n = 2$), but in whom a demyelinating process could not be confirmed. In all but 1 of the confirmed cases, the TNF-antagonist was discontinued because of the symptoms. We found no cases of PML. The mean age of the cases was 51 (range: 26 to 67) and the women-to-men ratio was 2:1. The incidence rate of demyelinating disease was 0.65 per 1000 patient-years (95% CI: 0.39-1.1). The rate in RA was 0.69 (95%CI: 0.36-1.32); the rate in AS was 0.70 (0.17-2.79), and the rate in PsA was 1.04 (95%CI: 0.34-3.24). The yearly rate of MS

Table 2 Incidence of Demyelination, Optic Neuritis, and Multiple Sclerosis in Patients Exposed to TNF Antagonists in BIOBADASER

Treatment	Demyelination	Optic Neuritis	Multiple Sclerosis	All
Infliximab				
n	5	2	1	8
Patient-years	11,237	11,237	11,237	11,237
IR	0.44 (0.19 to 1.07)	0.18 (0.04 to 0.71)	0.09 (0.01 to 0.6)	0.71 (0.36 to 1.42)
Etanercept				
n	3	2	0	5
Patient-years	7045	7045	7045	7045
IR	0.43 (0.14 to 1.32)	0.28 (0.07 to 1.14)	—	0.71 (0.3 to 1.71)
Adalimumab				
n	1	0	0	1
Patient-years	3143	3143	3143	3143
IR	0.32 (0.04 to 2.26)	—	—	0.32 (0.04 to 2.26)
All TNF-antagonists				
n	9	4	1	14
Patient-years	21,425	21,425	21,425	21,425
IR	0.42 (0.22 to 0.81)	0.19 (0.07 to 0.5)	0.05 (0.01 to 0.33)	0.65 (0.39 to 1.1)
General population, Spain (22 to 25)	—	—	0.02 to 0.04	—

IR, incidence rate per 1000 (95% confidence interval).

in different Spanish populations ranges from 0.022 to 0.038 (22-25). Table 2 shows the overall incidence rate of demyelination, optic neuritis, and MS in patients from BIOBADASER stratified by TNF-antagonist.

Cases of Demyelinating Diseases in the FEDRA Database

Twenty-one cases were found with at least 1 of the terms of the standard MedDRA query "demyelination" in patients treated with TNF antagonists (Table 3 gives a general description). Two cases were excluded; 1 patient with arthritis who developed trigeminus neuralgia and 1 patient who developed encephalomyelitis and a viral infection. Only 4 of these 21 cases had also been included in BIOBADASER.

Demyelinating Cases in the Literature

The search strategy identified 702 records (172 in MEDLINE and 530 in EMBASE, with 58 duplicates, 0 records in the Cochrane Library Plus). After screening selection criteria by title and abstract, only 65 references were selected for detailed review. Of these, 29 articles were excluded because they included either duplicated cases from subsequent reports, were unrelated to rheumatic diseases, or did not include any information on demyelinating cases. The 36 publications finally selected were case series or case reports of patients with inflammatory diseases treated with TNF antagonists. Three articles (8,26-28) reviewed the literature nonsystematically and contributed an additional case (index patient). Mohan and coworkers reported a series of 19 cases of neurologic events in patients treated with TNF-antagonist agents in December 2001 (8). Shin and coworkers reviewed all cases extracted from the FDA's Adverse Event Reporting System database of Guillain-Barre syndrome (GBS) and Miller-Fisher syndrome in patients treated with TNF-antagonists (27). Shin's review identified 15 patients who developed GBS following treatment with TNF antagonists. In the other nonsystematic review, 1 new case of optic neuritis was reported and 14 cases were reviewed (26,28).

In addition to these case series, a total of 48 cases of demyelinating disease (central or peripheral) have been published (Table 4): 13 optic neuritis, 11 demyelinating disease, 10 MS, 9 peripheral demyelinating disease, 3 GBS, and 2 transverse myelitis. All neurologic events were temporally related to therapy with TNF antagonists, with partial or complete resolution on discontinuation of the biologic. Demyelinating disease developed ex novo in all cases but 1 with a history of previous mononeuritis multiplex (29) and another with a previous diagnosis of GBS (30). In 2 cases there was a family history of MS (31-33). Twenty-three cases occurred while on treatment with infliximab, 21 with etanercept, and 4 with adalimumab.

Comparison of the Cases in the Three Data Sources

The age and gender distribution were similar in the 3 sources, but time of exposure to the TNF antagonist was longer in BIOBADASER (Table 3). In the 3 sources, 50% of the cases were RA patients and there were more cases of demyelination in PsA than in AS patients. Of note, the outcome of the adverse events differed between sources, with fewer cases recovering in BIOBADASER.

Table 3 Differences in the Demyelinating Cases Between the 3 Consulted Sources

	Case-reports[a]	FEDRA[b]	BIOBADASER[c]
N	48	19	14
Women, *n* (%)	34 (71)	10 (53)	9 (64)
Age, mean (SD)	45 (16)	49 (14)	51 (11)
Exposure time (yr), mean (SD)	0.73 (0.58)	0.96 (0.77)	1.44 (1.25)
Diagnosis, *n* (%)			
Rheumatoid arthritis	31 (65)	10 (53)	9 (64)
Ankylosing spondylitis	5 (10)	3 (16)	2 (14)
Psoriatic arthritis	6 (13)	4 (21)	3 (21)
Others	6 (13)	2 (11)	0 (0)
Treatments, *n* (%)			
Infliximab	23 (48)	11 (58)	8 (57)
Etanercept	21 (44)	6 (32)	5 (36)
Adalimumab	4 (8)	2 (11)	1 (7)
Type of demyelination, *n* (%)			
Multiple sclerosis	10 (21)	9 (47)	1 (7)
Optic neuritis	13 (27)	7 (37)	4 (29)
Demyelinating disease	11 (23)	2 (11)	9 (65)
Others	14 (29)	1(5)	0 (0.0)
Outcome, *n* (%)			
Recovered	24 (50)	7 (37)	5 (36)
Partially recovered	22 (46)	—	1 (7)
Not recovered	1 (2)	8 (42)[d]	7 (50)
Unknown	1 (2)	4 (21)	1 (7)

[a]Systematic literature review.
[b]Spanish pharmacovigilance system database.
[c]Spanish register of biologic drugs in rheumatic patients.
[d]Not recovered when the report was sent.

DISCUSSION

We investigated the characteristics and incidence of demyelinating cases in patients with rheumatic diseases treated with TNF antagonists. Notably, the information obtained depended on the source: literature review, spontaneous pharmacovigilance system, or a biologics registry, reflecting the different nature of the safety system and ratifying the more pragmatic view of the registries. As an example, MS represents nearly half of the cases reported to FEDRA, but only 7% of the BIOBADASER cases. This distribution reflects the common practicality of spontaneous reporting systems, in which notification covers mainly severe and worrying diseases, as opposed to drug registries, in which the complete spectrum of seriousness is covered.

Our data show that patients with rheumatic diseases treated with TNF antagonists developing demyelinating diseases tend to be older than patients with the primary demyelinating conditions, mainly in their thirties and more frequently men (34). This age pattern has also been reported in patients suffering from both conditions and not treated with TNF antagonists (14) and may characterize a distinctive phenotype. Interestingly, we found a higher frequency of demyelinating events in PsA compared with other diseases, although not statistically significant. This finding opens hypotheses that need to be tested in other settings.

Our study highlights that when considering demyelinating events as adverse reactions, we are assuming a temporal association that it is not such. It has been suggested that TNF antagonists may increase the risk of demyelinating diseases in patients with RA by about 30% (35). However, these data are not supported by the information gathered from the BIOBADASER registry. The short time from the start of the therapy to the development of demyelinating symptoms and the improvement of symptoms on discontinuation of the biological therapy are a feature common to cases from literature reports and spontaneous surveillance, but not from the registry. In BIOBADASER most cases appeared after several exposures, including long-term exposure, and did not necessarily improve after cessation of the biologic. The re-occurrence on rechallenge with the TNF antagonists in some reports could merely be explained by the common spontaneous or drug-induced relapsing-remitting episodes of MS, because relapses and progression define the MS phenotype.

Another important finding is that the estimated number of cases did not exceed the expected in the background population. The overall prevalence of RA and MS are 0.5% and 0.05%, respectively (22-25,36). The aggregation of both diseases in the same patient has been reported (11,13,14). This coincidence should be not surprising, because both AR and MS share similarities regarding genetic and pathogenic elements (37,38). In our study, the

Table 4 Description of Cases Recovered from the Systematic Literature Review

Case	Reference	Age/Sex	Dx	Anti-TNF	Time (mo)	Diagnosis	Treatment	Outcome
1	Pfuelle (41)	36/F	AS	ETA	6	MS	None	Complete recovery
2	Do (42)	46/F	RA	ETA	22	DD	Pulse MP	Partial recovery
3	Davis (43)	53/M	PsA	ETA	6	MS like	IFN-β+STE	Stable
4	Davis (43)	42/M	PsA	ETA	21	MS	No treatment	Partial recovery
5	Davis (43)	51/F	AS	ETA	18	MS like	No treatment	Partial recovery
6	Kameda (44)	66/F	RA	ETA	24	DD	Pulse MP	Partial recovery
7	Zalewska (45)	37/F	RA	ETA	10	DD	No treatment	Complete recovery
8	Silburn (46)	46/F	RA	INF	1.5	GB	No treatment	Complete recovery
9	Gómez-Gallego (47)	36/F	PsA	ETA	4	MS	Pulse MP	Partial recovery
10	Simsek (27)	31/F	RA	INF	4	ON	Pulse MP+STE	Compete recovery
11	Bidaguren (48)	76/F	RA	INF	20	ON	Pulse MP	Complete recovery
12	Bensouda-Grimaldi (49)	32/F	RA	ADA	23	MS+ON	Pulse MP	Partial recovery
13	Cay (30)	36/M	AS	ETA	6	ATM	Pulse MP	Complete recovery
14	Martínez-Taboada (50)	59/F	RA	ETA	1.5	DD+Vasculitis	None	Partial recovery
15	Ruiz-Jimeno (31)	47/F	PsA	INF	8	DD	Pulse MP+IVIG	Partial recovery
16	Al Saieg (51)	58/F	RA	ETA	>1 yr	MS+ATM	Pulse MP	Partial recovery
17	Tektonidou (52)	60/M	RA	INF	5	MMN	IVIG	Complete recovery
18	Tektonidou (52)	56/F	RA	INF	1.5	ASP	IVIG	Complete recovery
19	Shin (26)	56/M	RA	INF	15	GB (MF)	Pulse MP+IVIG	Partial recovery
20	Tauber (53)	12/F	JIA	ETA	2.5	ON	Pulse MP	Complete recovery
21	Tauber (53)	17/F	JIA	ETA	8	ON	Pulse MP	Complete recovery
22	Tauber (53)	21/F	JIA	ETA	18	ON	Pulse MP	Continued symptoms
23	Tauber (53)	18/M	JSpA	ETA	11	ON	Pulse MP	Complete recovery
24	Chung (54)	55/M	PsA	ADA	4	ON	Pulse MP	Complete recovery
25	Chung (54)	40/M	RA	ADA	12	ON	No treatment	Partial recovery
26	Jarand (55)	50/F	RA	INF	6	DP	IVIG	Partial recovery
27	Tanno (56)	56/M	RA	INF	1.5	DD	GC	Complete recovery
28	Tanno (56)	66/F	RA	INF	4	DD	GC	Partial recovery
29	Munteis-Olivas (57)	60/F	RA	INF	4	MS	No treatment	Stable
30	Bellesi (58)	40/F	RA	ADA	2	DD	Pulse MP	Partial recovery
31	Arias (59)	61/F	RA	INF	9	ATM	Gabapentin + Amitriptyline	Partial recovery
32	Titelbaum (60)	33/F	RA	ETA	24	MS	Pulse MP	Partial recovery
33	Freeman (61)	18/F	CD+AS	INF	12	DD	No treatment	Stable
34	Kunzmann (62)	5/F	Still's	ETA	12	DD	NR	NR
35	Richez (63)	73/F	RA	ETA	17	DP	No treatment	Partial recovery
36	Richez (63)	47/M	AS	INF	4	DP	No treatment	Partial recovery
37	Cocito (64)	40/F	RA	INF	9	MMN	IVIG	Complete recovery
38	Noguera-Pons (65)	55/M	RA	ETA	3	ON	Pulse MP	Partial recovery
39	Rodriguez-Escalera (66)	34/F	RA	INF	4	MMN	IVIG	Complete recovery
40	Richette (28)	41/F	RA	INF	8	MMN	Pulse MP	Complete recovery
41	Richette (28)	48/F	RA	INF	8 h	Progression MMN	Cyclophosph iv + GC	Partial recovery
42	ten Tusscher (67)	54/M	RA	INF	3	ON	Pulse MP	Stable
43	ten Tusscher (67)	62/F	RA	INF	3	ON	Pulse MP	Stable
44	ten Tusscher (67)	54/M	RA	INF	2	ON	Pulse MP	Stable
45	Cisternas (29)	34/M	PsA	INF	1	Recurrence GBS	IVIG	Complete recovery
46	Foroozan (10)	55/F	RA	INF	14	ON	Pulse MP	Complete recovery
47	Mohan (8)	48/M	RA	ETA	4	DD	Pulse MP	Partial recovery
48	Sicotte (9)	21/F	JIA	ETA	9	MS	Pulse MP	Partial recovery

Dx, diagnosis; M, male; F, female; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; ON, optic neuritis; DD, demyelinating disease; ATM, acute transverse myelitis; GBS, Guillain-Barré syndrome; MMN, multifocal motor neuropathy; DP, demyelinating polyneuropathy; MFS, Miller Fisher's syndrome; NR, not reported; TNF, tumor necrosis factor; JSpA, juvenile spondyloarthritis; MP, methylprednisolone; IFNβ, interferon-β; GC, glucocorticoids; IVIG, intravenous immunoglobulin; IV, intravenous; ASP, axonal sensory polyneuropathy.

estimated rate of demyelinating diseases does not differ from the background Spanish population [0.022 to 0.038 (22-25)].

Our study has several limitations that could explain some discrepancies. Spontaneous adverse drug reaction reporting (FEDRA database) is useful in identifying signals to be further investigated, but underreporting and selective reporting are the main caveats. Case reports are a major source for detecting rare adverse events, although they may represent a publication bias favoring a causal association of TNF antagonists with demyelinating diseases. A better approach would have been a meta-analysis of clinical trials, but there were no reports of demyelinating events. The reliability of the reporting of adverse events to registries increases with the nature of the adverse event. In the case of demyelinating diseases, report bias ("down-reporting") is very unlikely, especially given the awareness toward these particular adverse events. In fact, signs and symptoms suggestive of, but without a proven lesion, test, or image of demyelinating disease are frequently reported (almost 1 case per 1000), reflecting the alertness of the rheumatologists.

A drawback to this study is that it is impossible to confirm the association in an unexposed population of rheumatic diseases. The comparison cohort we used to test this type of hypothesis is formed only by RA (n = 789), and there were no cases of MS or demyelinating disease in the 5 years of follow-up (39). This is one of the reasons we decided to analyze the complete registry, not only the RA cohort.

In clinical trials, the use of TNF antagonists in patients with MS was associated with an increase in disease activity (40,41). This paradoxical failure and the precipitation of demyelinating events with TNF antagonists in MS may be explained by the following: (1) TNF antagonists do not readily penetrate the blood-brain barrier, enhancing disease activity via an increase in peripheral T-cell autoreactivity (42); (2) downregulation of the p75 TNF-α receptor related to autoreactivity (43); (3) downregulation of TNFR2, necessary for the proliferation of immature oligodendrocytes (34) and repair of damaged axons; or (4) downregulation of downstream cytokine production, ie, IL-10, and upregulation of IL-12 associated with MS disease activity (44). However, while these hypotheses could explain the failure of the TNF inhibition, they do not adequately explain the occurrence of new or worsened demyelinating symptoms in RA or Crohn's patients receiving anticytokine therapy.

In summary, the estimated rate of demyelinating diseases in patients with rheumatic diseases treated with TNF antagonists does not clearly differ from the expected rate in the population. If TNF antagonists were responsible for demyelinating diseases, it is likely that the resulting disorders were MS-like diseases, but do not strictly meet the criteria for MS. Moreover, the absence of a clear temporal association, together with the low rate, leads us to believe that the appearance of demyelination may be a matter of chance and may not reflect a true association with the treatment with TNF antagonists. Clinical differences between demyelinating cases in a national registry and 2 other pharmacovigilance sources could merely be explained by a selective reporting bias. Nevertheless, the unsettled association of demyelinating disease relapse calls for contraindication of TNF antagonists in patients suffering both a rheumatic and a demyelinating disease.

APPENDIX: BIOBADASER STUDY GROUP

The BIOBADASER Study Group includes the following:

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