CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: CAN WE MAKE A DIAGNOSIS IN PATIENTS NOT FULFILLING ELECTRODIAGNOSTIC CRITERIA?

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ABSTRACT

Objective: to identify the clinical and diagnostic investigations that may help supporting a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in patients not fulfilling the EFNS/PNS electrodiagnostic criteria.

Methods: we retrospectively reviewed the data from patients with a clinical diagnosis of CIDP included in a national database.

Results: we included 535 patients with a diagnosis of CIDP. This diagnosis fulfilled the EFNS/PNS criteria in 468 patients (87.2%) (definite in 430, probable in 33, possible in 3, while two had CISP). Sixty-seven patients had a medical history and clinical signs compatible with CIDP but electrodiagnostic studies not fulfilling the EFNS/PNS criteria for CIDP. These patients had similar clinical features and frequency of abnormal supportive criteria for the diagnosis of CIDP compared to patients fulfilling EFNS/PNS criteria. Two or more abnormal supportive criteria were present in 40 (61.2%) patients raising to 54 (80.6%) if we also included a history of a relapsing course as a possible supportive criteria. Increased cerebrospinal fluid proteins and response to immune therapy most frequently helped in supporting the diagnosis of CIDP. Response to therapy was similarly frequent in patients fulfilling or not EFNS/PNS criteria (87.3% versus 85.9%)

Conclusions: Patients with a clinical diagnosis of CIDP had similar clinical findings, frequency of abnormal supportive criteria and response to therapy compared to patients fulfilling EFNS/PNS criteria. The presence of abnormal supportive criteria may help supporting the diagnosis of CIDP in patients with a medical history and clinical signs compatible with this diagnosis but non-diagnostic nerve conduction studies.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and often disabling neuropathy with a prevalence ranging from 1 to 9 cases per 100 000 [1,2]. The cause of CIDP is still unclear even if several data point to an immune mediated pathogenesis, as also indicated by the frequent improvement of patients after immune therapies [3-6]. The majority of patients with CIDP has a mostly symmetric proximal and distal motor and sensory impairment with decreased or absent deep tendon reflexes and a progressive or relapsing course [3-6]. Several variants have been however described based on distribution of symptoms and signs broadening the spectrum of this disorder [3-7].

Diagnosis of CIDP can be challenging and, in recent years, several different sets of diagnostic criteria have been proposed with variable combinations of electrophysiological and clinical features [8-11]. Currently, the most widely accepted criteria are those recommended by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) [11] that were shown to provide the best combination of sensitivity and specificity (about 75% and 90%, respectively) for the diagnosis of CIDP compared with the other criteria [12-14]. These criteria allow however, this diagnosis only in the presence of demyelinating feature in at least one motor nerve. In most reported series, there is indeed a consistent proportion of patients who have the clinical features compatible with a diagnosis of CIDP but who do not fulfill the EFNS/PNS electrodiagnostic criteria [14] and, therefore, might be denied the access to effective therapy. In these patients, a clinical diagnosis of CIDP is often supported by the presence of abnormal ancillary investigations. It is not clear, however, which and how many supportive criteria may help in the diagnosis of these patients, and whether their clinical features and response to therapy are similar to those of the patients who fulfill the EFNS/PNS criteria.

We reviewed the data from patients with a medical history and clinical signs compatible with CIDP and electrodiagnostic criteria not fulfilling the EFNS/PNS electrodiagnostic criteria included in the Italian CIDP database to clarify whether the clinical features, disease course and treatment response was similar to patients fulfilling EFNS/PNS criteria and to identify the relevance of ancillary tests in supporting the diagnosis of CIDP.

PATIENTS AND METHODS

Database and study population

From January 2015 to June 2019, we enrolled 582 patients with a clinical diagnosis of CIDP in our web-based database (CINECA, Bologna, Italy). We excluded 24 patients for the presence of a different diagnosis and 23 patients for unavailable neurophysiological data. A total of 535 patients were included in the study. At the time of enrollment, 468 (87.5%) patients fulfilled the EFNS/PNS clinical and electrodiagnostic criteria for CIDP including 430 (92%) patients with a definite, 33 (7%) with a probable, and three (1%) with a possible diagnosis of CIDP. We also included among them two patients (0.4%) with a typical chronic immune sensory polyradiculopathy (CISP) [15] and normal motor conduction studies. The other 67 (12.5%) patients had a medical history and clinical signs compatible with the diagnosis of CIDP or one of its variants but did not fulfill the EFNS/PNS electrodiagnostic criteria. We reviewed the data from these patients and compared to those of patients fulfilling these criteria [16]. The Ethic Committee of each participating Center approved the study. All the patients gave written informed consent

Clinical assessment and ancillary tests

All patients were subjected to detailed clinical history including time of onset, distribution and progression of symptoms including weakness, sensory symptoms, ataxia, pain, cranial nerve impairment, autonomic dysfunction, and the presence and duration of concomitant diseases. The clinical evaluation at enrollment included assessment of muscular strength, sensory function, walking, and cranial nerves. Muscle strength was assessed with the Medical Research Council (MRC) scale [17], range 1-60. Neurological disability was evaluated with the INCAT scale [18], range 0-10.

The treating neurologist defined the course of the disease as progressive or relapsing. A relapsing course was defined as a clinical worsening after an initial improvement that was not related to a suspension or reduction of the dose of therapy. Some patients with a delayed worsening (> three months) after treatment suspension or reduction might have been however also included in this group. An acute onset of CIDP (A-CIDP) was also reported and defined as a neuropathy that was initially diagnosed as Guillain-Barré syndrome (GBS) but that continued to progress or relapse after more than two months from disease onset. The diagnosis of a typical or atypical CIDP phenotype was reviewed in all the patients by the coordinating Center at the time of the inclusion in the study according to our criteria [7]. We defined response to previously performed therapy as a subjective amelioration confirmed by the treating neurologist as an improvement of at least 2 points on the MRC sum score or one point on the INCAT score [19].

Results of cerebrospinal fluid (CSF) examination performed during the course of the disease were reported including total protein level and cell count. As to protein counts, we considered as upper reference limit 50 mg/dl for patients aged ≤50 years and 60 mg/dl for those aged >50 years [20]. The results of brachial/lumbosacral plexus and roots MRI examination were reported and defined by the local examiner of possible supportive value for the diagnosis of CIDP, if they showed an enlargement or T2-hyperintense signal and/or gadolinium enhancement [11]. The results

of nerve ultrasound (US) were considered of possible supportive value for the diagnosis of CIDP if the local examiner reported an enlargement of the examined nerves beyond their normal values [21]. The results of nerve biopsy, mostly of the sural nerve, were considered relevant for the diagnosis if the examiner reported signs of demyelination or remyelination by teased fiber analysis or electron microscopy or inflammatory cell infiltrates on paraffin sections.

The results of diagnostic nerve conduction studies (NCS) performed during the course of the disease were included. Motor nerve conduction studies were planned to be performed bilaterally in the median, ulnar, common peroneal and tibial nerves and included distal and proximal (up to the elbow in most patients) compound muscle action potential (CMAP) amplitude (onset to peak) and duration, motor conduction velocities (MCV), distal and proximal motor latencies and in most patients F-wave latency. Sensory conduction studies were planned to be performed bilaterally in the median, ulnar and sural nerves and included sensory action potential (SAP) amplitude, distal latency (DL) and conduction velocity (SCV). There was no definite time point for the examination since each Center was asked to include the most complete and diagnostic examination. Some patients also underwent somatosensory evoked potentials (SSEP) that were considered of diagnostic value if they reflected abnormal conduction velocity in proximal sensory fibers in the absence of signs of central nervous system disease. The reason for suspecting the diagnosis of CIDP beyond the results of nerve conductions studies was also reported in the Database by each center including the abnormality of any supportive criteria and a history of a relapsing course.

All the patients had been extensively investigated in each center for the presence of a possible alternative cause of the neuropathy by clinical and laboratory investigations in accordance with the EFNS/PNS guidelines [11]. Patients with serum IgM monoclonal gammopathy were excluded if they had increased titers of anti-myelin-associated glycoprotein (MAG) IgM antibodies (over 7000 Unit by Buhlman method in our laboratory). Patients with a concomitant disease

including diabetes and monoclonal gammopathy without anti-MAG antibodies were included in the study, as their presence does not exclude the diagnosis of CIDP according to EFNS/PNS criteria. In all the patients, we centrally reviewed the clinical features and the results of ancillary tests and classified the results of motor and sensory nerve conduction studies according to the EFNS/PNS criteria, to determine the diagnosis of definite, probable or possible CIDP [11].

Statistical analysis

Descriptive statistics were reported for the sample of patients with CIDP overall and separately for the two subgroups of patients fulfilling or not the EFNS/PNS diagnostic criteria. Categorical variables were described using frequencies and percentages, while continuous variables using mean, medians and ranges. We compared demographic and clinical features, including response to therapy, between different subgroups of patients with the chi-square or the Fisher's exact test for categorical variables, and the t-test or the Wilcoxon-Mann-Whitney test for continuous variables. We performed the analyses with IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp, USA).

RESULTS

Clinical findings and disease course

The 67 included patients were 45 men (67.2%) and 22 women (32.8%) (ratio: 2.0:1), aged 32 to 87 years (mean 60.5; median 62) with a mean age at onset of 52.2 years (median 55; range 15-77 years), a mean disease duration of 8.0 years (median 6; range 0.2-37 years) and a mean INCAT score of 2.4 (median 2; range 0-8). In 49 (73.1%) patients the clinical phenotype was of typical CIDP and in 18 (26.9%) of atypical CIDP (Table 1). The progression of the disease was relapsing in 33 patients (50%) and progressive in 33 (33%), while in one the data was missing. Two (3.3%) patients had an acute onset evolving in both into a relapsing course. None of the examined

demographic and clinical parameters significantly differed from patients with the EFNS/PNS criteria with the only exception of dysphagia or dysphonia that was more frequent in EFNS/PNS patients (Table 1).

Role of supportive criteria

A similar proportion of patients fulfilling or not the EFNS/PNS electrodiagnostic criteria had increased CSF proteins and comparable levels of the proteins (Table 2). Sensory nerve conduction abnormalities consistent with demyelination according to the EFNS/PNS criteria were more frequently found in patients with EFNS/PNS CIDP. Only one patient without EFNS/PNS criteria had delayed SSEP in the lower limbs. This patient also had reduced SCV in the ulnar nerve. Similarly frequent in patients fulfilling or not EFNS/PNS criteria were nerve biopsy findings consistent with demyelination or with inflammatory infiltrates and nerve or roots enlargement or enhancement by MRI or US. A similar frequent overall response to therapy was also observed between patients fulfilling (85.9%) or not (87.3%) the EFNS/PNS criteria with a similarly frequent response to IVIg, corticosteroids, plasma exchange or other immune therapies (Table 2).

The presence of abnormal supportive criteria for the diagnosis of CIDP (response to therapy, elevated CSF proteins, abnormal sensory electrophysiology, MRI/US abnormalities, demyelination/ inflammation on nerve biopsy) were examined in all patients not fulfilling electrodiagnostic criteria (mean number of supportive criteria examined 2.9, range 1 to 4) with a mean number of abnormal tests of 1.8 (range 1-4) (Table 3). Two or more supportive criteria were found in 41 patients (61.2%) while 12 (17.9%) patients had three or more supportive criteria for the diagnosis of CIDP. When we added the presence of a relapsing course to the supportive criteria, 54 (80.6%) patients had at least two supportive criteria (Figure 1) including 26 (38.8%) with three of more criteria (Table 3). Since the diagnosis of CIDP should be considered before starting therapy, when we

excluded response to therapy from the supportive criteria, two or more supportive criteria were found in 12 (17.9%) raising to 32 (47.8%) if we added the presence of a relapsing course.

Electrodiagnostic studies

The number of examined motor nerves was lower in patients not fulfilling the EFNS/PNS electrodiagnostic criteria (mean 4.8, median 5, range 2-8) than in EFNS/PNS patients (mean 5.6, median 6, range 2-8; $p < 0.0015$). There was no difference in the time of executing electrodiagnostic in relation to the onset of symptoms between patients fulfilling (5.1 years) or not (3.9 years; $p > 0.05$)) electrodiagnostic criteria. At least four motor nerves were however examined in 50 not EFNS/PNS patients (74.6%) and six or more nerves in 26 (38.8%) patients. There was no difference between patients with less than four motor nerve examined and those with four or more nerves examined with the only exception of a lower disability in the first group and a slightly more frequent occurrence of autonomic symptom (Table 3). The frequency of each abnormal supportive criteria was similar in the two groups as was the proportion of patients with two or more abnormal supportive criteria and the response to therapy.

We also examined whether the presence of minor, non-diagnostic signs of demyelination could favor the diagnosis in not EFNS/PNS patients. These were found in 39 (73.1%) patients (14 in upper limb nerves, 23 in lower limb nerves and 2 in both) including: 30-49% reduction of proximal-to-distal CMAP amplitude reduction in one nerve excluding the tibial nerve (6 patients); 20-29% reduction of proximal-to-distal CMAP amplitude in one (5 patients) or more nerves (2 patients) excluding the tibial nerve and the site of nerve compression; 40-49% proximal-to-distal CMAP amplitude in one tibial nerve (3 patients); 20-29% reduction of motor conduction velocity in one (11 patients) or two nerves (5 patients) including 10 with normal or less than 20% distal CMAP amplitude reduction (5 in upper and 5 in lower limb nerves) and 6 with a more pronounced reduction of CMAP amplitude (all in lower limb nerves); F-waves absent in two or more nerves (5

patients) in the absence of other demyelinating features; 40-49% increased distal latency in one nerve (2 patients). When required [10], the distal CMAP amplitude of the negative peak was higher than 20% of the lower normal limit. The other 28 patients either had minimal sign of possible demyelination (10-20% reduction of motor conduction velocity or 20-30% reduction of proximal to distal CMAP amplitude or 30-39% in tibial nerve)(17 patients) or absence or reduced amplitude of distal CMAP (11 patients), in upper (3 patients) or lower (22 patients) limbs or both (3 patients). There was no difference between patients with or without minor signs of demyelination with the only exception of a higher number of male and a higher frequency of abnormal sensory conduction studies in patients with these signs (Supplementary Table).

DISCUSSION

Since the first formal definition of CIDP by Dyck et al. in 1975 [22], at least 15 diagnostic criteria were proposed with different combinations of clinical, electrophysiological, laboratory, and biopsy features. Different comparison studies confirm that the best combination in terms of sensitivity/specificity [12-14] is offered by the EFNS/PNS criteria [11], which are currently used in most clinical trials in CIDP. A number of supportive investigations were included in these criteria to improve the diagnostic certainty in patients not fulfilling the electrodiagnostic criteria. These investigations support however the diagnosis in patients already fulfilling a possible or probable diagnosis of CIDP but do not allow this diagnosis in patients not having demyelinating features in at least one motor nerve.

In our series of 535 patients with a diagnosis of CIDP or one of its variants, 468 (87.5%) patients fulfilled the diagnostic criteria of the EFNS/PNS, while 67 (12.5%) had a medical history and clinical signs compatible with CIDP with electrodiagnostic studies not fulfilling the EFNS/PNS criteria. None of these patients had clinical or laboratory signs of other possible causes for their

neuropathy. These data are in line with the reported sensitivity of these criteria [12-14]. Rajabally and colleagues [14] reported, for instance, that 81.3% of the patients with CIDP fulfilled the EFNS/PNS criteria for definite or probable CIDP. This percentage is similar to the proportion of our patients with definite or probable CIDP (86.5%).

Our patients not fulfilling the EFNS/PNS criteria had a similar gender distribution, age at onset, symptoms at onset and during the course of the disease, typical or atypical presentation, disease duration, and INCAT score at enrollment in comparison to EFNS/PNS patients. The progression of the disease was relapsing in about half of the patients in both groups. Even if this relatively high figure is similar to other series [23-24] it might reflect the absence of clear definition of relapse, so that patients with a delayed worsening (> three months) after treatment suspension or reduction might have been considered to have a relapsing form in both groups. The only difference between the two groups was a slightly lower frequency of dysphagia or dysphonia in not EFNS/PNS patients and a lower frequency of sensory conduction studies consistent with demyelination in this group that is probably consistent with the difference observed in motor nerve conduction studies. There was also no significant difference in the proportion of each abnormal supportive criteria between the two groups. Most importantly, not EFNS/PNS patients had a similarly frequent overall response to therapy and to each individual therapy compared to EFNS/PNS patients. Even if this data should be considered with caution in a retrospective study, in all our patients, the treating neurologist confirmed the subjective amelioration using clinically relevant measures [19].

When we analyzed the factors that might have contributed to the diagnosis of CIDP beside the medical history and clinical presentation, we found that 41 (61.2%) patients had at least two supportive criteria for this diagnosis. This figure raised to 54 (80.6%) if we also considered a relapsing course as a possible supportive criteria for the diagnosis. Even if a relapsing course is part of the clinical definition of CIDP we think that its consideration as possible supportive criterion is

justified by its occurrence in only few other neuropathies including vasculitis, acute porphyria and episodes of exposure to toxic agents. The distinction with hereditary neuropathy with liability to pressure palsy may be more difficult given the similar presence of signs of demyelination and conduction block. The combination however of clinical history, presence of other supportive abnormalities, response to therapy and absence of familial history might help in the distinction from these neuropathies. A better definition of relapse in CIDP might be also necessary to uniform the data from different series. The number of supportive criteria in our patients might have been even higher if we consider that nerve US or MRI and nerve biopsy were only performed in a minority of patients to improve the diagnostic definition. This could explain why an invasive test like nerve biopsy was performed in a higher proportion of patients not fulfilling (16.4%) than fulfilling (7.5%, $p = 0.0321$) EFNS/PNS criteria while noninvasive tests like nerve US or MRI were performed in a similar proportion of patients (12.9% and 13.8%).

One limit of this study is the lower number of examined motor nerve in patients not fulfilling than in those fulfilling the EFNS/PNS electrodiagnostic criteria. Most of not EFNS/PNS patients had however (73%) four or more motor nerves examined and 38.8% at least six nerves. It is not possible to exclude that some of these patients might have fulfilled the EFNS/PNS electrodiagnostic criteria with a more extensive and complete electrophysiological examination inclusive of a more proximal nerve stimulation in the upper limbs. There was no difference between patients with four of more nerves examined or less suggesting that a more complete study was not always associated with an improved diagnosis. Similarly, there was no difference between patients with or without minor non-diagnostic signs of demyelination indicating that the use of less restrictive electrodiagnostic criteria did not permit to implement the sensitivity of the diagnosis for CIDP.

Given our data, we think that in patients with a medical history and clinical signs compatible with CIDP and no sign of a possible alternative diagnosis, the presence of two supportive criteria might support a diagnosis of possible clinical CIDP (40.3% in our series), three criteria for probable (29.9%) and four (10.4%) for definite clinical CIDP, especially when response to immune therapy is well documented and a better definition of relapse would be available. We also think that the presence of at least two supportive criteria may also justify the initiation treatment in a previously untreated patient with a medical history and clinical signs compatible with CIDP. This would have allowed initiation of therapy in almost 50% of our patients if we also considered a history of a relapsing course.

Even if these criteria may favor the access to the diagnosis and therapy in a number of patients not fulfilling the EFNS/PNS electrodiagnostic criteria, it is also possible that they might increase the risk of over-diagnosis in CIDP especially in patients with an atypical presentation or with only axonal changes on nerve conduction studies [24,25]. We think however that an objective assessment of the medical history and clinical presentation of the patients, the exclusion of other possible causes for the neuropathy and an accurate search for possible supportive criteria for the diagnosis of CIDP might reduce this risk and favor the access to treatment of patients that would be otherwise denied a possibly effective therapy. This opportunity should be considered in the ongoing revision of the EFNS/PNS (now EAN/PNS) aimed at improving the sensitivity of the diagnostic criteria for CIDP.

Limitations of this study include its retrospective nature and the lack of a control population of patients not affected by CIDP. Moreover, US/MRI and nerve biopsy were not routinely performed, so that the percentages of clinical CIDP patients with at least two supportive criteria could be even higher than in our analysis. Data on response to therapy should be also considered with caution considering the retrospective nature of this study. This response was however similar

to what reported in the literature [27-32], probably reflecting the fact that the study was performed in centers with expertise in immune mediated neuropathies. Despite these limitations, we think that this study provide the opportunity to verify the usefulness and the critical issues related to the use of current diagnostic criteria for CIDP and supports the opportunity of the revision of these criteria.

Contributors: ENO and GL conceived, organized and designed the study, reviewed and commented on the statistical analysis, wrote the first draft of the report and reviewed the report. FM, DC, RF, CB, MF, LB, GA, GC, SJ, AM, AC, AMC, GAM, AMC, GS, MC, ML, GL, TR, GC, EB, PED, EB, LS, ST, MR, SCP, AS, LL, AT, LP, GM contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. DC, FM, GC, MS, PEM, ML and LS, reviewed an discussed the conclusion of the study.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

LEGENDS:

Table 1: comparison of demographic and clinical findings in patients with CIDP fulfilling or not EFNS/PNS criteria.

Table 2: comparison of diagnostic and therapeutic findings in patients with CIDP fulfilling or not EFNS/PNS criteria.

Table 3: comparison of demographic, clinical, diagnostic and therapeutic findings in patients with CIDP not fulfilling EFNS/PNS criteria in relation to the number of motor nerves examined.

Supplementary Table: comparison of demographic, clinical, diagnostic and therapeutic findings in patients with CIDP not fulfilling EFNS/PNS criteria in relation to the presence of minor signs of demyelination

Figure 1: Number of supportive criteria (SC), including (A) or not including (B) a relapsing course, in 67 patients with clinical CIDP not fulfilling EFNS/PNS electrodiagnostic criteria (numbers in brackets refer to number of patients).

Conflicting Interests

E.N.O. reported personal fees for Advisory or Scientific Board from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, LFB, France, Astellas, the Netherlands, outside the submitted work and travel grants to attend Scientific Meeting from Baxter, Grifols, Kedrion, and Novartis, Italy. P.E.D. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. G.L. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. D.C. reported honoraria for lecturing from Shire, CSL Behring, and Kedrion and travel grants to attend scientific meeting from Shire, Kedrion, and CSL Behring. E.P. reported travel grants to attend scientific meetings from CSL Behring. R.F. has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. M.C. reported travel grants to attend scientific meetings from Kedrion. A.M. reported travel grants from Kedrion and CSL Behring to attend scientific meeting. C.B. has served on scientific advisory boards for Pfizer and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. G.C. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. B.F. reported travel grants to attend scientific meetings from CSL Behring and liberal contribution from CSL Behring for the neuromuscular diseases centre, outside the submitted work. A.C. reported travel grants to attend scientific meetings from Kedrion. M.L. reported honoraria for scientific board from Pfeizer and Alnylam and travel grants from Pfeizer, Grifols and Kedrion to attend scientific meeting. L.S. reported personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. F.M. reported personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. G.C. reported honoraria for lecturing and travel grants to attend scientific meetings from Kedrion. M.F. has served on scientific advisory boards for CSL Behring and Sarepta Therapeutics and has received travel grants from Sanofi Genzyme, Kedrion, Baxter and CSL Behring to attend scientific meeting. S.J. reported research grants from Grifols, outside this work, and travel grants from Grifols and Kedrion. G.A.M. reported consulence fees and travel fundings from CSL Behring, Kedrion, Shire and Grifols. G.A. reported honoraria for lecturing from Kedrion and Sanofi-genzyme, travel grants from Kedrion, Sanofi-Genzyme and LJ Pharma. G.M. reported consulence fees and travel fundings from CSL Behring, Kedrion, Shire and Grifols. The other authors declare no conflict of interest.

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