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ORIGINAL COMMUNICATION

Botulinum toxin therapy for treatment of spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force

Dirk Dressler[1] · Roongroj Bhidayasiri[2] · Saeed Bohlega[3] · Abderrahmane Chahidi[4] · Tae Mo Chung[5] · Markus Ebke[6] · L. Jorge Jacinto[7] · Ryuji Kaji[8] · Serdar Koçer[9] · Petr Kanovsky[10] · Federico Micheli[11] · Olga Orlova[12] · Sebastian Paus[13] · Zvezdan Pirtosek[14] · Maja Relja[15] · Raymond L. Rosales[16] · José Alberto Sagástegui-Rodríguez[17] · Paul W. Schoenle[18] · Gholam Ali Shahidi[19] · Sofia Timerbaeva[20] · Uwe Walter[21] · Fereshte Adib Saberi[22]

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Abstract Botulinum toxin (BT) therapy is an established treatment of spasticity due to stroke. For multiple sclerosis (MS) spasticity this is not the case. IAB-Interdisciplinary Working Group for Movement Disorders formed a task force to explore the use of BT therapy for treatment of MS spasticity. A formalised PubMed literature search produced 55 publications (3 randomised controlled trials, 3 interventional studies, 11 observational studies, 2 case studies, 35 reviews, 1 guideline) all unanimously favouring the use of BT therapy for MS spasticity. There is no reason to believe that BT should be less effective and safe in MS spasticity than it is in stroke spasticity. Recommendations include an update of the current prevalence of MS spasticity and its clinical features according to classifications

✉ Dirk Dressler
dressler.dirk@mh-hannover.de

[1] Movement Disorders Section, Department of Neurology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

[2] Chulalongkorn Centre for Excellence on Parkinson's Disease and Related Disorders, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[3] Department of Neurology, King Faisal Specialist Hospital, Riyadh, Kingdom of Saudi Arabia

[4] Basic and Clinical Neurosciences Research Laboratory, University Medical School of Marrakech, Marrakech, Morocco

[5] University of Sao Paulo, Sao Paulo, Brazil

[6] Department of Neurology, Dr. Becker Rhein-Sieg-Klinik, Nümbrecht, Germany

[7] Department of Adult Neuro-Rehabilitation, Adult Botulinum Toxin Clinics, Centro de Medicina de Reabilitação de Alcoitão, Alcabideche, Portugal

[8] Department of Neurology, University of Tokushima, Tokushima, Japan

[9] Centre de Rééducation et Medicine Physique, Hôpital du Jura, Porrentruy, Switzerland

[10] Department of Neurology, Palacky University, Olomouc, Czech Republic

[11] Department of Neurology, Hospital de Clínicas José de San Martín, University of Buenos Aires, Buenos Aires, Argentina

[12] Clinic 'Cecil Plus', Moscow, Russia

[13] Department of Neurology, Bonn University, Bonn, Germany

[14] Department of Neurology, Ljubljana University Medical Centre, Ljubljana, Slovenia

[15] Department of Neurology, University of Zagreb, Zagreb, Croatia

[16] Department of Neurology and Psychiatry, University of Santo Tomas Hospital, Manila, Philippines

[17] Department of Neurology, Universidad de Monterrey, Monterrey, Mexico

[18] Department of Neurology, Maternus-Klinik für Rehabilitation, Bad Oeynhausen, Germany

[19] Department of Neurology, Movement Disorders Clinic, Rasoul-e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

[20] Scientific Research Institute of Neurology, Moscow, Russia

used in movement disorders. Immunological data on MS patients already treated should be analysed with respect to frequencies of MS relapses and BT antibody formation. Registration authorities should expand registration of BT therapy for spasticity regardless of its aetiology. MS specialists should consider BT therapy for symptomatic treatment of spasticity.

Keywords Botulinum toxin · Therapeutic use · Spasticity · Multiple sclerosis · Review · Recommendations · IAB-Interdisciplinary Working Group for Movement Disorders

Introduction

Multiple sclerosis (MS) is one of the most common neurological disorders of young adults with 149 out of 100.000 Germans being affected [28]. This equals about 2.5 million MS patients worldwide [41]. MS can affect not only the central nervous system white matter, but also its grey matter. It can, therefore, produce a wide range of motor disorders, reaching from paresis to apraxia or fatigue. Spasticity may be one of them. Around two-third of MS patients are suffering from spasticity [47]. Almost half of them are rating their spasticity as moderate or severe [47]. Conventional treatment of spasticity includes baclofen, tizanidine, diazepam and dantrolene as oral drugs [5]. Continuous intrathecal baclofen application through implanted pumps can be helpful for severe spasticity, especially in the legs [20]. Peripheral surgery is reserved for few special cases. Intramuscular phenol injections are only rarely performed. Botulinum toxin (BT) was originally introduced in the early 1980s as a compound reducing various muscle hyperactivity syndromes. Later on it was also used to reduce hyperactivity of exocrine glands and, most recently, to reduce migraine pain. Other pain conditions are under investigation. Spasticity has long been one of the main muscle hyperactivity syndromes treated with BT [19].

When spasticity is caused by stroke, a large body of literature supports the use of BT [60]. Subsequently, formal registrations for the use of BT to treat stroke spasticity have been granted by the regulatory authorities in most major countries and robust sales figures indicate BT's actual use for this indication. When spasticity, however, is caused by MS, the literature is scarce, formal registrations are usually lacking and the actual clinical potential seems underused. Therefore, IAB-Interdisciplinary Working Group for Movement Disorders [1] formed a task force to explore the use of BT for treatment of MS spasticity.

[21] Department of Neurology, Rostock University, Rostock, Germany

[22] IAB-Interdisciplinary Working Group for Movement Disorders, Hamburg, Germany

Methods

Literature search

The literature search was performed on PubMed (National Center of Biomedical Information, United States National Library, Medicine and National Institutes of Health). Search date was July 19th, 2016. The search included all references published up to this point of time. The search was performed along three axes with the following search words:

Axis 1 Botulinum toxin, botulinum neurotoxin, onabotulinumtoxinA, incobotulinumtoxinA, abobotulinumtoxinA, rimabotulinumtoxinB.

Axis 2 Multiple sclerosis, encephalomyelitis disseminata, MS.

Axis 3 Spasticity.

All publications retrieved had to contain at least one item on each axis. There were no exclusion criteria. The retrieved publications were classified according to the following categories: Randomised Controlled Trial, Interventional Study, Observational Study, Case Study, Review and Guideline.

Results

Literature search

The literature search produced 55 publications containing the above-mentioned search words. Table 1 gives an overview about the retrieved publications.

Randomised controlled trials

Three of the publications were Randomised Controlled Trials. They are shown in Table 2. Snow et al. [62] was the

Table 1 Number of studies retrieved from PubMed for the current literature search

Study type	Number of studies
Randomised controlled trial	3
Interventional study	3
Observational study	11
Case study	2
Reviews	35
Guidelines	1
Total	55

Table 2 Randomised controlled trials retrieved from PubMed for the current literature search

Study	Design	Methods	Results
Snow et al. [62]	RCT	9 pts with hip-adductor spasticity due to MS Ashworth scale, hygiene scale Botox 400MU	BT reduces Ashworth and hygiene scales
Grazko et al. [25]	RCT	4 pts with leg spasticity, 1 pt with arm spasticity due to MS Ashworth scale 8 pts with rigidity	BT reduces Ashworth scale
Hyman et al. [29]	RCT	74 pts with hip-adductor spasticity due to MS knee distance, pain score, hygiene score, spasm frequency adverse effects Dysport 500MU/1000MU/1500MU	Dysport reduces hip spasticity no clear dose effect adverse effects

RCT randomised, placeno-controlled trial, *pt/pts* patient/patients

Table 3 Interventional Studies retrieved from PubMed for the current literature search

Study	Design	Methods	Result
Giovannelli et al. [23]	Parallel groups investigator blinded	38 pts with MS spasticity control/BT/BT and physiotherapy groups Ashworth scale, visual analogue scale	BT improves both dimensions, better effect in BT and physiotherapy group
Barnes et al. [4]	Parallel groups investigator blinded	192 pts with upper limb spasticity 1% due to MS dilution 20/50MU/ml disability scale, Ashworth scale Xeomin®	No dilution effect
Paolini et al. [48]	Parallel groups	42 pts with MS spasticity role of vibration in BT therapy	BT therapy and vibration improve spasticity

BT botulinum toxin, *pt/pts* patient/patients, *MS* multiple sclerosis

first article published. The authors demonstrated that Botox® reduces MS hip-adductor spasticity as measured by the Ashworth scale and improves hygiene as measured by a hygiene scale [62]. Gradzko et al. demonstrated Botox® induced reduction of MS arm and leg spasticity as measured by the Ashworth Scale. Additionally, they detected reduction of Parkinson's disease rigidity as measured by the United Parkinson's Disease Rating Scale [25]. Hyman et al., again, demonstrated reduction of MS hip-adductor spasticity as measured by knee distance, pain score, hygiene score and spasm frequency score. There was no clear dose effect correlation [29].

Interventional studies

Three publications retrieved were Interventional Studies. They are shown in Table 3. Giovannelli et al. demonstrated that BT therapy alone improves MS spasticity as compared to a control group. Further improvement, however, is seen when BT therapy is combined with physiotherapy [23]. Barnes et al. could not detect an effect of different Xeomin® dilutions on upper limb spasticity of various aetiologies. Only 2 of their 192 patients suffered from MS [4]. Paolini et al. found that BT therapy as well as vibration may improve spasticity in MS [48].

Observational studies

Eleven publications were Observational Studies. They are shown in Table 4. Most studies were on spasticity of different aetiologies including MS. Eight studies demonstrated spasticity improvement after BT therapy usually documented by Ashworth scale often complimented by visual analogue scales, spasm frequency scores, pain scores, or hygiene scores or singular functional tests [8, 14, 33, 35, 46, 54, 63, 64]. Two studies pursued other goals. One study demonstrated that the Barthel index does not correlate with spasticity improvement [16]. Another

Table 4 Observational Studies retrieved from PubMed for the current literature search

Study	Design	Methods	Result
Konstanzer et al. [35]	Follow-up	11 pts with MS/stroke spasticity in arms, legs, feet Ashworth scale, pain scale, hygienic Scale Dysport® 1000-1200MU in arms Dysport® 1680-2000MU in unilateral hip adductor	10/11 pts improved on each scale
Borg-Stein et al. [8]	Follow-up	2 pts with MS spasticity Ashworth scale, functional status	2/2 pts improved in dimensions
Kerty and Stien [33]	Follow-up	5 patients with MS hip-adductor spasticity clinical examination	2/5 pts improved
Turhanoglu et al. [64]	Follow-up	23 pts MS/stroke/myelitis spasticity in arms and legs 5 due to MS Ashworth scale, spasm frequency score, visual analogue scale	23/23 pts improved on each scale
Opara et al. [46]	Follow-up	20 pts with spinal cord injury/MS paraspasticity Ashworth scale, visual analogue scale for pain, Rivermead mobility index, Repty functional index	Most pts improve
Sobolewski [63]	Follow-up	12 pts with spinal cord leg spasticity Dysport® 1000/2000MU Botox® 200/400MU	Thigh and triceps surae passive range of motion improve
Dionyssiotis et al. [16]	Follow-up	Pts with spasticity due to multiple aetiologies including MS	Barthel index does not correlate with spasticity improvement
Cioncoloni et al. [14]	Follow-up	20 pts with MS/stroke spasticity Ashworth scale, walking test	BT therapy improves gait
Phadke et al. [49]	Follow-up	99 pts with stroke/MS/cerebral palsy leg spasticity examination of BT total dose per injection series	BT total dose in MS spasticity > cerebral palsy spasticity> stroke spasticity
Schramm et al. [54]	Follow-up	508 pts with stroke/traumatic brain injury/MS/cerebral palsy/anoxia spasticity	No difference in efficacy and safety of BT therapy between different diseases
Cheung et al. [13]	Follow-up	39 pts with stroke/MS spasticity examination of spasticity and spasticity modifiers	MS spasticity more modulated by modifiers

MS multiple sclerosis, *pt/pts* patients

study showed that BT total doses are different in spasticity of different aetiologies [49]. Highest doses were necessary in MS, lower ones in cerebral palsy and stroke.

Case studies

Two publications were Case Studies. Sławek et al. described a patient with paraspasticity successfully treated with BT. After disease progression to tetraspasticity therapy was intensified to intrathecal baclofen with favourable result [61]. Daelen et al. described a patient with severe tetraspasticity and bruxism successfully treated with BT in the M. masseter bilaterally [15].

Reviews

Thirty-five publications were Reviews. They are summarized in Table 5. Four Reviews were dealing with general treatment of MS and mentioned BT as a spasticity treatment [42–44]. Five Reviews were dealing with treatment of MS spasticity and mentioned BT as one treatment option [5, 27, 55–57]. Two Reviews were dealing with symptomatic treatment of MS and mentioned BT as a spasticity treatment [38, 50]. One Review was dealing with BT and MS [36], 1 with MS and spasticity mentioning BT as a spasticity treatment [9]. Three Reviews were dealing with treatment of spasticity and mentioned BT as a treatment of MS spasticity [12, 34, 51]. Five Reviews were dealing with BT for symptomatic treatment of MS and mentioned BT as a treatment option for spasticity [11, 26, 30, 31, 67]. Most of those sReviews also discussed other uses of BT in MS patients including treatment of hypersalivation, hyperhidrosis, bladder dysfunction, eye motility disorders, tremor and proctologic conditions. Fourteen Reviews were dealing with BT for spasticity treatment and mentioned BT as a treatment option in MS spasticity [2, 6, 7, 10, 22, 32, 39, 40, 45, 58, 59, 65, 66, 68].

Table 5 Reviews retrieved from PubMed for the current literature search

Topic	Authors	Remarks
General treatment of MS	Nicholas and Chataway [42]	
$n = 4$	Nicholas and Chataway [43]	
	Nicholas and Rashid [44]	
	Yeh [69]	Children
Treatment of MS spasticity	Shakespeare et al. [55]	
$n = 5$	Shakespeare et al. [56]	
	Beard et al. [5]	
	Shakespeare et al. [57]	
	Heinzlef and Monteiol-Roch [27]	
Symptomatic treatment of MS	Metz [38]	No note on BT bladder therapy
$n = 2$	Pöllmann et al. [50]	No note on BT bladder therapy
		focus on pain conditions
MS and BT	Lamotte and Thoumie [36]	No note on BT bladder therapy
$n = 1$		
MS and spasticity	Bussel et al. [9]	
$n = 1$		
Treatment of spasticity	Kita and Goodkin [34]	
$n = 3$	Rekand [51]	
	Chang et al. [12]	
BT for symptom-matic treatment of MS	Wissel and Entner [67]	BT for hip adduction
$n = 5$	Kabus et al. [31]	
	Jost [30]	BT for hyperhidrosis mentioned
		BT for hypersalivation mentioned
		BT for proctologic problems mentioned
	Habek et al. [26]	BT bladder disorders mentioned
		BT for various MS pain conditions mentioned
		BT for tremor?
		BT for eye motility disorders?
	Cameron et al. [11]	BT for bladder disorders mentioned
		BT for tremor?
BT for spasticity treatment	Calne [10]	
$n = 14$	Simpson [59]	
	Yablon [68]	
	Moore [40]	
	O'Brien [45]	
	Fève [22]	
	Bell and Williams [6]	
	Baba et al. [2]	
	Sheean [58]	
	Bensmail and Roche [7]	
	Ward [66]	
	Keam et al. [32]	
	Walker et al. [65]	Application guidance
	Moeini-Naghani et al. [39]	

BT botulinum toxin, *MS* multiple sclerosis, *n* number of studies

Guidelines

One publication was a Guideline based on recommendations from committees of the Spanish Society of Neurology and the German Neurological Society [24]. In this publication BT was mentioned as a potential treatment for MS spasticity in selected cases.

Discussion

Spasticity in MS

74% of all MS patients complain of spasticity; 47% present with spasticity with an Ashworth Score ≥ 2 [3]. 10% of all MS patients are estimated to be candidates for BT therapy [3]. Spasticity in MS, therefore, is a highly relevant symptom of MS.

Conventional treatment of MS spasticity

Due to the high prevalence of spasticity in MS a considerable number of antispastic therapies emerged over the years including oral baclofen, tizadinine, benzodiazepam/clonazepam, dantrolene, gabapentine, clonidine, intrathecal baclofen and, most recently, cannabidiol/tetrahydrocannabinol (nabiximols, Sativex®). Adjuvant treatments include orthopaedic surgery, physiotherapy, occupational therapy and other physical therapies. Despite the number of conventional treatment options for MS spasticity, treatment effects are often only mild and treatment of more severe forms remains a challenge.

Principal suitability of BT therapy for MS spasticity

Classically, spasticity is defined as 'a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome' [37]. This definition has its merits in neurophysiological discussions. However, it describes only one of the many motor phenomena occurring when supranuclear motor system lesions occur. This was the reason why a broader definition was introduced recently [17]. The spastic syndrome is now defined as a combination of central paresis and various forms of muscle hyperactivity including spasticity as such, dystonia, rigidity and spasms [17]. All of those muscle hyperactivities are responsive to BT therapy. The element with least clinical relevance is probably spasticity in its original definition. It may, as a matter of fact, even be considered an examination artefact.

Treating spastic syndromes, it has to be taken into account that muscle hyperactivity may have positive functional aspects, such as stabilising paretic limbs, and that treating muscle hyperactivity does not improve co-existing paresis. Treating spastic syndromes with BT has a time window: When in the further course of the disease contractures arise, spastic postures turn fixed and BT therapy becomes ineffective. Timely treatment, therefore, is encouraged [52].

BT's mode of action is based upon the blockade of the cholinergic neuromuscular synapse [18]. Additional effects on muscle spindles are discussed [53]. Transsynaptic spinal transport of active BT has not been demonstrated so far. BT's action on increased alpha-motoneuron activity should therefore be independent from the kind of supraspinal excitation, be it dystonic or spastic in origin. It should also be independent from the level of supranuclear lesion, be it spinal or supraspinal. Therefore, BT efficacy should not be affected by the kind of supraspinal excitation (dystonic, spastic, tremor, etc.) nor by the localisation of the lesion (spinal, supraspinal), let alone the underlying pathological process (ischemic, traumatic, encephalitic). Altogether, there is no reason why BT should not act upon MS spasticity in a similar way as it is acting upon stroke spasticity.

BT therapy for MS spasticity/literature search

BT has long been used in symptomatic treatment of MS and spasticity has been the earliest, largest and best documented indication. Other muscle hyperactivity phenomena have been tried including tremor, ataxia, myokymia, nystagmus, internuclear ophthalmoplegia and dysphagia, however, so far with ambiguous results. Various forms of bladder dysfunction affecting the detrusor vesicae, the sphincter internus and the sphincter externus have recently been investigated. With robust positive effects, several of these conditions have become licenced indications. Experimentally, various MS-associated pain syndromes have also been treated with BT.

Our literature search produced a robust body of studies on the use of BT in MS spasticity. All 3 Randomised Controlled Trials [25, 29, 62] and all 3 Interventional Studies [4, 23, 48] demonstrated the efficacy of BT to treat hip, arm and leg spasticity in MS. Additional physiotherapy may be helpful. All 11 Observational Studies [8, 13, 14, 16, 33, 35, 46, 49, 54, 63, 64] and all 2 Case Studies confirmed these results [15, 61]. All 35 Reviews dealing with different aspects of MS stated a principal suitability of BT for treatment of MS spasticity.

Altogether, the literature on BT therapy for MS spasticity is scarcer than that on stroke spasticity. The study quality is similar although large registration studies are missing in MS spasticity. All publications unanimously

favour the use of BT therapy for MS spasticity. One guideline includes BT therapy as one of the treatment options for MS spasticity [24].

Current situation of BT therapy for MS spasticity

There is no robust published data on the extent of clinical use of BT therapy, neither for MS spasticity, nor for stroke spasticity. Internal data of the BT manufacturers may exist in stroke spasticity; in the off-label use of MS spasticity they would be extremely vague. Regional differences of BT use for spasticity are considerable [21]. The limited number of publications and overall sales figures of BT drugs together with the general feeling that MS spasticity is underrepresented in our BT clinics suggests an under-use of this treatment option.

Causes for the current situation may be manifold. (1) The current prevalence of MS spasticity may be lower than suggested by prevalence data not adapted to the recent improvements in neuromodulatory therapies. (2) Prevalence figures on MS spasticity may erroneously include motor dysfunction unresponsive to BT such as apraxia, ataxia and fatigue. (3) In most countries use of BT therapy is closely linked to the drug's registration status as only full formal registration for a specified indication guarantees reimbursement by the insurance systems. So far, BT therapy for spasticity is not a registered indication in most countries. Only very recently, registration of BT therapy for spasticity is considered by few registration authorities without restricting the underlying aetiology to stroke only. BT's high cost reimbursement and registration restrictions are an issue and probably the major obstacle to use BT therapy for MS spasticity.

Unaddressed issues

As large double-stranded protein BT drugs are antigenic. With this they could interfere with the MS relapse frequency. Conversely, increased immunological activity in MS patients could increase the risk of BT antibody formation. Both aspects have not been studied so far.

Recommendations

As an initial step, formal studies should provide exact data on the current prevalence of MS spasticity and its clinical features according to the classification used in movement disorders. In parallel, immunological long-term data on MS patients already treated should be analysed with respect to MS relapse frequency and frequency of BT antibody formation. With this, registration authorities should consider expansion of the current registration status of BT drugs for spasticity to aetiologies other than stroke. Alternatively, specific registration studies should be initiated by the BT manufacturers to limit the off-label problem. Attempts to expand registrations to include MS spasticity are currently under way. MS specialists should consider BT therapy for symptomatic treatment of spasticity.

Compliance with ethical standards

Conflicts of interest Dressler D: DD received honoraria for services provided to Allergan, Ipsen, Merz, Desitin, Syntaxin, Abbvie, Medtronic, St Jude, Boston Scientific, Almirall, Bayer, Sun, Teva, UCB, IAB-Interdisciplinary Working Group for Movement Disorders. He is shareholder of Allergan and holds patents on botulinum toxin and botulinum toxin therapy. Bhidayasiri R: RB is supported by Thailand Research Fund, Chulalongkorn Academic Advancement into its 2nd Century Project, and Ratchadapiseksompoj grant of Chulalongkorn University. He is an advisory board member of Britannia Pharmaceuticals; receives honoraria from Novartis, Ipsen, GlaxoSmithKline, and BL Hua pharmaceuticals; and royalties from Wiley-Blackwell and Humana press. He is an associate editor of BMC Neurology and Journal of Clinical Movement Disorder; and on the editorial board of Parkinsonism and Related Disorders journal and Journal of the Neurological Sciences. Bohlega S: SB has nothing to declare. Chahidi A: AC has nothing to declare. Ebke M: ME has nothing to declare. Jacinto J: JJ has received financial support from Ipsen, Allergan and Merz companies as an expert advisor, lecturer/speaker, researcher, peer trainer in the fields of spasticity management and neuro-rehabilitation. He owns no shares nor has any other relation with the above-mentioned companies. Kaji RE: RK received honoraria from Ipsen, GSK, Eisai and Merz to lecture in symposiums, and training courses and for advisory board participation. He participated in several clinical research trials from Merz. He holds a patent on A2NTX. Kanovsky P: PK has received speakeŕs honoraria from Merz, Ipsen, Allergan, Medtronic, Novartis, AbbVie and Desitin. Micheli F: FM has nothing to declare. Orlova O: OO is scientific consultant for Allergan, Ipsen, Merz, MSD. Paus S: SP received honoraria for services provided from Allergan, Ipsen and Merz. Pirtosek Z: DP received compensation for speaker related activities from Pharmaswiss and Medis. Sagástegui-Rodríguez A: ASR has nothing to declare. Schoenle PW: PWS has nothing to declare. Shahidi GA: GAS has nothing to declare. Tae MC: MCT received honoraria from Ipsen, Allergan and Merz to lecture in symposiums, and in training courses and to participate in advisory boards. He participated in clinical research from Ipsen. He did not receive any research funding and has no financial interest in BoNT. Timerbaeva S: ST has received speaker fees and meeting sponsorship from Ipsen and Merz companies. Walter U: UW has received research funds from Merz Pharmaceuticals and speaker honoraria and travel grants from Abbvie, Bayer Vital, Ipsen Pharma, Merz Pharmaceuticals and Pfizer. Adib Saberi F: FAS received honoraria for services provided from Abbott, Abbvie, Almirall, Allergan, Bayer, Desitin, Dynamed, Ipsen, Medtronic, Merz, Sintetica, Sun, Teva and UCB.

Ethical standard The study was performed according to the ethical standards statement.

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