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REVIEW

Treating relapsing–remitting multiple sclerosis: therapy effects on brain atrophy

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Abstract Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with a complex and heterogeneous pathology that may ultimately lead to neurodegeneration and brain atrophy. Brain volume loss in MS is known to occur early in the disease course and to be clinically relevant, as it has been related to disability progression. Nowadays, brain volume loss is relatively easy to measure with different automated, reproducible and accurate software tools. Therefore, most of (if not all) the newest clinical trials have incorporated brain volume outcomes as a measure of treatment effect. With this review, we aimed to update and summarize all existing data regarding brain volume and RRMS treatment in clinical trials as well as in open-label observational studies of drugs with positive results in its primary outcome in at least one phase III trial as of March 2014.

Keywords Brain atrophy · MS therapy · Interferon · Monoclonal · Oral

Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with a complex and heterogeneous pathology consisting in a combination of inflammation, demyelination, gliosis and axonal loss. These processes may ultimately lead to neurodegeneration, tissue damage and brain atrophy [1]. Brain atrophy is a common and early feature in MS patients; it occurs at an accelerated rate when compared with healthy controls, and it is clinically relevant as it has been related to disability [2, 3]. Current methods for measuring brain volume (BV) are usually automated softwares that either use a segmentation-based approach [such as the statistical parametric mapping (SPM) or SIENAX] for cross-sectional data or a registration-based approach (such as the structural imaging evaluation using normalization of atrophy—SIENA) for longitudinal analysis. BV measures yielded by the above-mentioned programs will be: percentage of BV change (PBVC) for the SIENA software, normalized BV (NBV) for SIENAX, and brain parenchymal fraction (BPF), grey matter fraction (GMF) and white matter fraction (WMF) for SPM software. These methodologies have gone through extensive testing and provide us now with an accurate, reproducible and efficient way of measuring in vivo this clinically relevant neurodegenerative process [4].

Thus, it is not surprising that recent clinical trials have incorporated BV outcomes as a measure of treatment effect [5]. A number of the disease modifying drugs available for MS patients, specially the newest ones, have shown to improve brain atrophy accrual when compared to placebo. In recent years, the amount of drugs released to the market for treating relapsing–remitting MS (RRMS) patients has grown considerably. In this review, we aimed to summarize all existing data regarding BV and RRMS treatment in clinical trials as well as in open-label observational studies of drugs with positive results in its primary outcome in at least one phase III trial as of March 2014. Most of the studies reported in this review have used the software packages mentioned above, with their respective measures, but in some, in-house software packages have been used.

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Effect of therapies on BV: clinical trials data

Interferon beta

Brain volume analysis in subcutaneous (sc) interferon beta (IFN-β) clinical trials on clinically isolated syndromes (CIS) patients, yielded contradictory results. Compared to placebo, patients treated with a weekly dose of 22 μg sc IFN-β-1a in the ETOMS clinical trial, had a lower BV loss during the 2-year period analysed (PBVC: −1.18 versus −1.68 %; $p = 0.0031$) [6]. Surprisingly, the REFLEX clinical trial, evaluating the same IFN-β formulation, found no differences in BV loss over 2 years in patients receiving either weekly or three times a week high dose (44 μg) of sc IFN-β-1a as compared to the placebo arm [7]. In fact, patients receiving the highest frequency of interferon treatment seemed to have the largest loss of BV during the 2-year period of observation [7]. As for the sc IFN-β-1b clinical trial, BV results were only reported at year 3 and 5 after inclusion to the study [8, 9]. The study showed no differences in BV loss when comparing early versus delayed treatment, but no strict comparison to placebo was carried out [8, 9] (Table 1a). BV data for intramuscular (im) IFN-β-1a in CIS patients is not available.

Regarding RRMS treatment, the pivotal trial of im IFN-β-1a was the first to report atrophy outcomes [10]: although no significant differences were noted during the first year of treatment, IFN-β-treated patients presented lower BV loss during the second year of treatment as compared to placebo (−0.23 % in IFN-β-treated patients versus −0.51 % in the placebo arm, $p = 0.03$). When comparing first and second year of treatment, BV loss occurred at a different rate in IFN-β-treated patients with a greater volume loss occurring in the first year of treatment while there was no difference in BV loss rate between the two 1-year periods in the placebo arm. Along these lines, the European dose comparison study [11] evaluated BV changes during the first 3 years after starting im IFN-β-1a yielding similar results: a higher decrease of BPF occurred during the first year of treatment with the largest BV loss taking place in the first 4 months of therapy (Tables 1b, 2). The authors of these two studies evaluated the presence of inflammation as a possible confounder of subsequent BV loss and results were only partially in agreement. In one of the studies a correlation between the number of gadolinium-enhancing lesions at baseline and in-trial BV loss was observed but no significant correlation was found between the in-trial change in gadolinium-enhancing lesion volume and in-trial BV loss. Whereas in the other study, the rate of BV loss during the first months of treatment was paralleled by a drop in the number of gadolinium-enhancing lesions [10, 11]. The PRISMS clinical trial, evaluating two doses of sc IFN-β-1a versus placebo for treating RRMS patients, analysed BV measures in a long-term follow-up of up to 8 years [12]. Bearing in mind all the confounders inherent to these long-term designs, there were no differences in BV from baseline to last follow-up visit between all three arms. However, it is worth noting that, as previously described in the REFLEX CIS trial, during the double-blind phase (first 2 years) as well as when changing from placebo to active treatment in the open-label phase (from 2 to 4 years) BV loss was greater in the 44-μg group. The two pivotal clinical trials of IFN-β-1a [10, 12] found that, independently of treatment allocation, patients presenting higher disability progression were also those having greater BV loss than patients who did not progress. Data regarding treatment effect on BV loss for sc IFN-β-1b clinical trials in RRMS has not been published.

Glatiramer acetate

Glatiramer acetate (GA) demonstrated its efficacy for treating CIS patients in the PRECISE clinical trial [13]. The primary analysis of brain MRI outcomes allowed a strict comparison with placebo as it was performed using only the scans obtained before presenting a second relapse; with this measure the authors tried to correct for the confounding factor of starting open-label therapy in patients with RRMS regardless of the original group in which they were allocated. Compared to placebo, GA failed to prove reduction in BV loss measured as PBVC (−0.38 versus −0.33 %) [13]. However, a pre-planned open-label analysis showed that early treatment with GA significantly reduced brain atrophy when compared to patients with delayed treatment onset adjusting for study exposure (−0.99 versus −1.28 %, $p = 0.021$) [14] (Table 1a).

The first report of GA effects on BV in RRMS was in a subcohort of patients participating in the GA US Trial; in this small cohort, GA significantly reduced the rate of BV loss in the 2-year treatment period [15]. The initial analysis of the European/Canadian GA trial, measuring BV on a central portion of the brain with a semi-automated segmentation technique, showed no differences between placebo and GA-treated patients [16]. A posterior assessment of the same trial but using the SIENA software, showed a protective effect of GA in BV decrease at the end of the observation period (18 months); this beneficial effect was mainly due to a reduction of BV loss during the open-label phase in early treated patients [17]. These differences were no longer held when evaluating BV loss at 5 years after study entry [18] (Tables 1b, 2). The FORTE trial that evaluated two doses of GA (20 versus 40 mg administered daily) found no differences in BV measures between low- and high-dose treatment arms [19].

Table 1 Effect of therapies on brain volume: randomized clinical trials

(a) Data on clinically isolated syndromes

Drug	Clinical trial	Characteristics	Measure[a]	Results[b,c]
IFN-β-1a	ETOMS	Phase III, $n = 166$, 2 years Weekly sc 22 μg vs placebo	PBVC (SIENA)	30 % reduction in IFN-β-treated arm
	REFLEX	Phase III, $n = 517$, 2 years Weekly sc 44 μg vs TIW sc 44 μg vs placebo	PBVC (SIENA)	No significant differences
IFN-β-1b	BENEFIT	Phase III, $n = 468/n = 358$ Extension study at 3 and 5 years: early vs delayed Rx	PBVC (SIENA)	No significant differences between early or delayed Rx onset, no comparison with placebo
Glatiramer acetate	PRECISE	Phase III, $n = 481$, 2 years or LOV	PBVC (SIENA)	No significant differences (in the core study) 28 % reduction in early vs delayed Rx onset

(b) Data on relapsing–remitting multiple sclerosis

Drug	Clinical trial	Characteristics	Measure[a]	Results[b,c]
Injectable therapies				
Interferon beta 1a	AVONEX pivotal	Phase III, $n = 172$, 2 years im IFN-β vs placebo	BPF change	0–1 year: no significant differences 1–2 years: 55 % reduction in IFN-treated arm
	PRISMS	Phase III, $n = 382$, 6 years sc IFN-β-1a 44 μg vs sc IFN-β-1a 22 μg vs placebo 2 years, then open label	BPV change	BL to 6 years: no significant differences
Glatiramer acetate	Eur/Canadian GA Trial	Phase III, $n = 207$, 18 months/5 years GA vs placebo 9 months, then GA open-label	PBVC (SIENA)	0–9 months: no significant differences 9–18 months: 40 % reduction for early Rx 0–18 months: 25 % reduction in GA-treated arm 0–5 years: no significant differences in early vs delayed Rx
	US GA Trial	Phase III, $n = 27$ (subcohort), 2 years	BPF change	77 % reduction in GA-treated arm
	FORTE	Phase III, $n = 980$, 1 years GA 20 vs 40 μg	PBVC (SIENA)	No significant differences between two doses
Interferon and glatiramer acetate	REGARD	Phase III, $n = 460$, 2 years sc IFN-β-1a 44 μg vs GA	PBVC (SIENA)	BL to 2 years: 13 % reduction in GA-treated arm BL to 1 year: 8 % reduction in GA-treated arm[d] 1–2 years: 22 % reduction in GA-treated arm[d]
	BEYOND	Phase III, $n = 2096$, 2 years sc IFN-β-1b 500 μg vs sc IFN-β-1b 250 μg vs GA	PBVC (SIENA)	BL to 2 years: no significant differences BL to 1 year: greater volume loss for IFN-treated arm[e] 1–2 years and 2–3 years: no significant differences
	COMBIRx	Phase III, $n = 1008$, 3 years im IFN-β-1a vs GA vs im IFN-β-1a+ GA	GMF, WMF, CSF change	No significant differences
Oral drugs				
Fingolimod	FREEDOMS	Phase III, $n = 1033$, 2 years FTY 0.5 mg vs FTY 1.25 mg vs placebo	PBVC (SIENA)	Overall, 30 % reduction in pooled FTY-treated arms
	TRANSFORMS	Phase III, $n = 1153$, 1 year FTY 0.5 mg vs FTY 1.25 mg vs im IFN-β-1a	PBVC (SIENA)	FTY 0.5 mg: 31 % reduction FTY 1.25 mg: 33 % reduction
		Phase III, $n = 799$, 1 year extension phase FTY 0.5 mg and FTY 1.25 mg open-label	PBVC (SIENA)	FTY 0.5 mg: 51 % reduction FTY 1.25 mg: 62 % reduction
	FREEDOMS II	Phase III, $n = 1033$, 2 years FTY 0.5 mg vs FTY 1.25 mg vs placebo	PBVC (SIENA)	Overall, 45 % reduction in FTY-treated arms

Table 1 continued

(b) Data on relapsing–remitting multiple sclerosis

Drug	Clinical trial	Characteristics	Measure[a]	Results[b,c]
Dimethyl-fumarate	DEFINE	Phase III, $n = 540$, 2 years Dimethyl-fumarate BID vs TID vs placebo	PBVC (SIENA)	6 months to 2 years: 30 % reduction in the BID dose arm, negative results for the TID dose
	CONFIRM	Phase III, $n = 681$, 2 years Dimethyl-fumarate BID vs TID vs placebo, GA as active comparator	PBVC (SIENA)	BL to 2 years: 30.2 % reduction in the BID dose arm ($p = 0.064$), negative results in the TID dose and GA arms BL to 1 year: no significant changes 1–2 years: *32.2* % reduction in the BID dose arm, 32.2 % in the TID dose arm ($p = 0.075$), 28.8 % reduction in the GA arm ($p = 0.080$)
Teriflunomide	TEMSO	Phase III, $n = 1074$, 2 years Teriflunomide 7 mg vs 14 mg vs placebo	BPF, GMF, WMF changes	BPF and GMF change: No significant differences WMF: 83 % (7 mg) and 164 % (14 mg) relative change in teriflunomide-treated arms
Laquinimod	ALLEGRO	Phase III, $n = 1106$, 2 years Laquinimod vs placebo	PBVC	33 % reduction in laquinimod-treated arm
	BRAVO	Ph. III, $n = 1331$, 2 years Laquinimod vs im IFN-β-1a vs placebo	PBVC	28–34 % reduction in laquinimod-treated arm
Monoclonal antibodies				
Natalizumab	AFFIRM	Phase III, $n = 942$, 2 years Natalizumab vs placebo	BPF change	BL to 2 years: no significant differences BL to 1 year: 40 % greater atrophy in NAT-treated arm 1–2 years: 44 % reduction in NAT-treated arm
	SENTINEL	Phase III, $n = 1003$, 2 years IFN-β-1a im+ natalizumab vs IFN-β-1a im+ placebo	BPF change	BL to 2 years: no significant differences BL to 1 year: 19 % greater atrophy in NAT-treated arm[f] 1–2 years: 23 % reduction in NAT-treated arm
Alemtuzumab	CAMSS223	Phase II, $n = 334$, 3 years Alemtuzumab 12 mg vs 24 mg vs sc IFN-β-1a 44 μg	BPF change	72 % reduction in alemtuzumab-treated arm[g]
	CARE-MS-I	Phase III, $n = 581$, 2 years Alemtuzumab 12 mg vs sc IFN-β-1a 44 μg	BPF change	42 % reduction in alemtuzumab-treated arm
	CARE-MS-II	Phase III, $n = 840$, 2 years Alemtuzumab 12 mg vs 24 mg vs sc IFN-β-1a 44μg	BPF change	24 % reduction in pooled alemtuzumab-treated arms

BID two times a day, *BL* baseline, *BPF* brain parenchymal fraction, *BPV* brain parenchymal volume, *FTY* fingolimod, *GA* glatiramer acetate, *GMF* grey matter fraction, *IFN-β* interferon beta, *im* intramuscular, *LOV* last observed value before conversion to clinical definite *MS*, *mg* milligrammes, *μg* micrograms, *PBVC* percentage of brain volume change, *sc* subcutaneous, *SIENA* structural imaging evaluation using normalization of atrophy, *TID* three times a day, *TIW* three times a week, *Rx* treatment, *vs* versus, *WMF* white matter fraction

[a] If not stated, the software used was either not described or property packages were used (for more details, refer to the original article)

[b] Only significant differences are reported as percentage of reduction on BV loss compared to placebo and for the whole duration of the trial if not otherwise stated

[c] If the percentage of BV loss reduction was not reported in the original article, it was calculated as: 1 − (absolute brain volume loss for treatment arm/absolute brain volume loss for placebo arm)

[d] No p value reported

[e] Data reported only in graphic format, no exact numbers reported to calculate percentage of reduction

[f] $p = 0.058$

[g] $p = 0.05$

Table 2 Immediate and delayed therapy effects on brain volume changes in the double-blind phase of relapsing remitting multiple sclerosis trials

Drug	Global effect on brain volume[a]	Immediate effect on brain volume[b]	Delayed effect on brain volume[c]	Able to cross blood–brain barrier
Placebo-controlled studies				
Interferon beta 1a	No	No	Yes	No
Glatiramer acetate	No	No[e]	NA[f]	No
Fingolimod	Yes	Yes	Yes	Yes
Dimethyl-fumarate	Yes[g]	No[h]	Yes[h]	No
Teriflunomide	No	No	No	No
Laquinimod	Yes	NA	NA	Yes
Natalizumab	No	No	Yes	No
Active comparator[d]				
Interferon vs glatiramer acetate	Yes (GA)[i]	Yes (GA)[i]	Yes (GA)[i]	No
Fingolimod vs im IFN-β-1a	Yes (FTY)	Yes (FTY)	NA[j]	Yes (FTY)
Alemtuzumab vs sc IFN-β-1a 44 µg	Yes (AL)	NA[k]	NA[k]	No

AL alemtuzumab, *BID* two times a day, *FTY* fingolimod, *GA* glatiramer acetate, *IFN-β* interferon beta, *im* intramuscular, *NA* not applicable, *sc* subcutaneous, *vs* versus

[a] For the whole duration of the double-blind phase

[b] During the first 6–12 months of therapy

[c] After 12 months of therapy

[d] Drugs with significantly superior beneficial effects appear in brackets

[e] Baseline to 9 months

[f] Open-label data, a significant positive effect of glatiramer acetate on brain volume change was observed in months 9–18 in the early treatment arm

[g] Only for the BID dose in the DEFINE clinical trial; brain volume was assessed for the 6–24 month period

[h] Only for the BID dose in the CONFIRM clinical trial; no data available for the DEFINE clinical trial

[i] Data only from REGARD clinical trial, no *p* value reported. No significant differences were observed in the BEYOND and COMBIRx clinical trials

[j] No data available beyond 12 months

[k] The two CARE-MS trials only assessed brain volume changes from baseline to 24 months

Three large studies have compared IFN-β formulations and GA, showing similar performance for both drugs in clinical and MRI outcomes [20–22]. Brain atrophy was assessed in all three trials, one study could demonstrate a significant reduction in BV loss for GA-treated patients as compared to sc IFN-β-1a [20], but no differences were observed in the other two [21, 22] (Tables 1b, 2). Noteworthy, in all these three trials most of the BV loss occurred during the first 6–12 months of therapy.

Natalizumab

Natalizumab was the first monoclonal antibody approved for the treatment of MS after proving its efficacy in two phase III clinical trials. Both trials reported similar results regarding atrophy data and demonstrated again an interesting pattern of BV loss in the active arm: compared to placebo, natalizumab-treated patients presented greater BV loss during the first year of the trial, whereas significantly lower rates of BV decrease during the second year of treatment were observed [23, 24]. This was interpreted by the authors as an initial pseudoatrophy effect and a later protective effect of natalizumab in preventing brain atrophy [23, 24], and is also consistent with the similar pattern observed in some IFN-β trials (Tables 1b, 2).

Fingolimod

Fingolimod was the first oral drug approved to treat MS patients; three phase III clinical trials (FREEDOMS, FREEDOMS II and TRANSFORMS) demonstrated its efficacy not only regarding inflammation parameters but also in reducing BV loss [25–27]. Compared to placebo, fingolimod significantly reduced BV loss down to 30–45 %

after 2 years of treatment and this reduction was observed as early as 6 months after treatment onset [25, 27], specially in patients without baseline gadolinium-enhancing lesions [28] (Tables 1b, 2). Patients with baseline inflammation showed higher rates of BV loss during the first year of therapy, but this BV loss was never greater than the placebo arm [28]. Compared to im IFN-β-1a, patients receiving fingolimod also presented less BV loss during the first year of treatment [26] (Tables 1b, 2). These differences were held when subgroup analyses were performed [29]. In the extension study of the TRANSFORMS trial, patients switching from im IFN-β-1a to fingolimod treatment reduced their BV loss rate and no differences in BV loss between the core and the extension phase for patients continuing on fingolimod were observed [30].

Newest oral drugs

Results of brain atrophy for both phase III clinical trials with dimethyl-fumarate have been recently published [31, 32]. In the DEFINE clinical trial, comparing dimethyl-fumarate versus placebo in RRMS, and using the 6-month MRI as baseline for BV estimation, dimethyl-fumarate administered twice a day (BID) significantly reduced BV loss as compared to placebo; surprisingly, results for the three times a day (TID) posology on brain atrophy resulted negative [31]. In the CONFIRM trial, BV loss was analysed at different time-points: from baseline to the end of the trial (2 years), from baseline to year 1 and from year 1 to year 2. Compared to placebo, the BID dose seemed to reduce BV loss from baseline to year 2 (-0.660 vs. -0.945; $p = 0.0645$) and significantly reduced BV loss during the last year of follow-up (year 1 to year 2 of the clinical trial). Neither the TID dose nor glatiramer acetate significantly reduced BV loss at any point compared to placebo, although a trend towards statistical significance was observed from year 1 to year 2 for both drugs [32] (Tables 1b, 2).

Regarding teriflunomide, BV measures were only reported for the phase III TEMSO clinical trial: both doses of teriflunomide (7 and 14 mg.) failed to demonstrate a reduction in BV loss as compared to placebo [33] (Tables 1b, 2). However, when analysing not only global BV loss, but also tissue-specific BV changes, a significant reduction of white matter (WM) loss for both doses of teriflunomide as compared to placebo was observed [34].

As for laquinimod, its effect on BV loss was assessed in two phase III clinical trials [35, 36]. In the ALLEGRO clinical trial, adjusting for the baseline number of gadolinium-enhancing lesions, laquinimod significantly reduced BV loss as compared to placebo [35]. In the BRAVO study an active control arm with im IFN-β-1a for descriptive analysis was included: compared to placebo, laquinimod demonstrated a protective effect on BV loss reduction; conversely, IFN-β-1a failed to protect against BV loss, even showing non-significant greater reductions in BV compared to placebo [36] (Tables 1b, 2).

Newest monoclonal antibodies

Brain volume effects of alemtuzumab were first analysed in the phase II clinical trial CAMSS223: compared to 44 μg sc IFN-β-1a, alemtuzumab-treated patients showed a reduction in BV loss during the 3 years of the trial. BV changes occurring in the last 2 years of follow-up were also analysed (12–36 months) to find an even larger protective effect of alemtuzumab on BV loss [37]. Similar results, favouring alemtuzumab-treated patients compared to 44 μg sc IFN-β-1a, were obtained in both phase III CARE-MS-I and CARE-MS-II clinical trials [38, 39] (Tables 1b, 2). It is worth mentioning that brain volume loss reduction relative to 44 μg sc IFN-β-1a was more marked for treatment-naïve patients (about 40 % reduction in CARE-MS-I vs. 25 % reduction in CARE-MS-II) [38] and for patients originally randomized to the 24 mg arm (CARE-MS-II) [39].

Effect of therapies on BV: open-label observational studies

Interferon beta and glatiramer acetate

First open-label reports on BV changes under treatment were performed with the two formulations of sc IFN-β and with no control group [40, 41]. Both studies found that a greater BV loss occurred during the first months of therapy with a posterior slow down, specially after the second year of treatment [40, 41]; these findings were not modified by the presence of IFN-β neutralizing antibodies [41]. In one study, BV loss occurring during the first 6 years of therapy moderately correlated with EDSS worsening during the same time period; however, the authors did not find any early MRI variable that could predict disability progression over time [40]. More recent open-label studies did include a control group consisting of RRMS patients who decided not to start any treatment [42–44]. Despite the limitations of open-label studies, all injectable DMDs were shown to reduce global BV loss [42–44] and grey matter (GM) atrophy [42, 43] as compared to patients who did not receive any treatment. Whereas one of the studies seemed to favour IFN-β treatment on preventing GM pathology (specially development of new cortical lesions) [43], another study showed a larger effect of GA on reducing global BV [44]. Only one study assessed the effect of BV loss in predicting treatment response; the authors of this

study found that BV loss occurring during the first year of IFN-β therapy significantly increased the risk of presenting treatment failure at year 3 [45].

Natalizumab

Similar to what has been described in natalizumab clinical trials [23, 24], three observational studies with no control group confirmed that most of the BV loss occurring while on natalizumab treatment takes place during the first months of therapy, and found that it was related to baseline clinical [46] and radiological [47], [48] disease activity. Specifically, the number of baseline gadolinium-enhancing lesions predicted global and WM but not GM volume loss during the first [47] and second [48] year of therapy. In a study comparing natalizumab-treated patients with patients treated with injectable therapies (IFN-β and GA) and to untreated patients, natalizumab significantly reduced the number of new cortical lesions as well as cortical thinning over a 2-year treatment period [49]. In one study, the reduction in global and cortical volume loss was associated with a lower cognitive deterioration during the same period [50].

Discussion

Using automated techniques to measure BV changes, differences between placebo and treated arms have been shown in randomized clinical trials for some of the presently available disease modifying MS therapies; head-to-head trials have also shown superiority of some drugs over active comparators. Even though BV measures have been shown to be accurate and reproducible, a number of issues should be taken into account when interpreting therapy effects on BV changes.

Among methodological aspects, it is worth mentioning the evolution of analysis techniques as well as improvements in the acquisition of images; as it has been shown for the GA trial in RRMS, improvements in the analysis techniques may increase the power of the studies so as to observe previously undetectable treatment effects [15, 16]. Even more, it should be taken into consideration that some of the earliest trials do not feature BV data because of the insurmountable difficulties of multicentre analyses of such kind at that time. Another important aspect refers to the methodology used to obtain BV change estimates, as a number of automated techniques have been used and both BPF (obtained with a number of different software tools) and PBVC measures have been obtained. Although most techniques have demonstrated to be accurate and reproducible [51], segmentation-based techniques (used in a number of studies reported here) are not as robust as registration-based techniques for longitudinal studies [52] and, in any case, the global magnitude of treatment effect cannot be compared across trials. Other physiological and disease-related factors that can influence BV changes should also be taken into account; in this regard, a well-known source of variation is the hydration status or the presence of on-going inflammation at treatment onset. Patients participating in clinical trials or starting treatment in clinical practice are usually active patients with clinical relapses and presence of MRI activity as demonstrated by gadolinium-enhancing lesions. Resolution of this inflammation will lead to an initial accelerated BV loss that has been described as a 'pseudoatrophy' effect [5]. Along these lines, drugs with a high impact on inflammation, such as natalizumab [23, 24, 46–48], fingolimod [28] or high-dose IFN-β [7, 12], will tend to produce larger than placebo BV decreases during the first months of therapy (specially in patients presenting with gadolinium-enhancing lesions [28, 47, 48]) that, at least in part, may be not related to true tissue damage.

It is also worth mentioning that therapy effects on BV loss in CIS patients may be even more difficult to interpret, not only because of the design of the clinical trials, but also because of specific factors related with disease pathophysiology at the early stages. This may end up resulting in contradictory findings for the same drug [6, 7]. CIS patients who will present a second attack and thus, convert to clinical definite MS (CDMS) will be also having greater BV loss [53, 54]; however, placebo patients who develop CDMS while on the clinical trial will be switched to the treatment arm before trial termination; if this is not taken into account, the placebo arm may end up contaminated with active therapy effects on BV. Lastly, when CIS occurs it is usually accompanied of brain inflammation that, as stated before, may affect BV loss during the subsequent follow-up.

Obviously, it is also very important to recognize that treatment effects on BV may be different not only because of the methodological issues stated before but also because of specific aspects of the different drugs mechanism of action. Whereas all MS treatments have been shown to have an effect on the immune system that ultimately leads to decreased inflammation and which in consequence should decrease central nervous system damage, a neuroprotective effect, as measured by BV changes, has only been confirmed for a number of them. Neuroprotection, or the preservation of neuronal structures and its function, can be achieved by an indirect mechanism (due to the reduction of central nervous system damage) or to a direct mechanism (by increasing tissue resistance to critical damage or by promoting tissue repair). We could speculate that some of the drugs that have demonstrated a greater impact on BV loss, such as fingolimod, laquinimod or alemtuzumab have also been shown to have a direct neuroprotective effect,

either by promoting secretion of neurotrophic factors [55–57], blocking the production of nitric oxide [58] or promoting myelin repair [59]. Some of these drugs, such as fingolimod and laquinimod, may have the capacity of crossing the blood–brain barrier and may exert part of their potential neuroprotective effect directly into the central nervous system [60–62]; in any case, penetration in the CNS does not ensure the existence of a neuroprotective effect and, on the contrary, neuroprotection could also be exerted through mechanisms initiated in the periphery [63]. However, the effect of these potential neuroprotective drugs on progressive forms of the disease still has to be demonstrated and, in fact, preliminary data coming from the INFORMS trial of fingolimod in primary progressive multiple sclerosis have been reported negative; interestingly, coupling of such negative brain volume results with negative results on the primary outcome (disability progression) in spite of positive effects on lesion-related parameters seems to emphasize the importance of BV outcomes. On the other hand, IFN-β preparations and natalizumab which have no or little capacity to cross the blood–brain barrier, have shown to have either no or little immediate effect on BV loss, and may probably exert their neuroprotective effect only by reducing brain inflammation and preventing lymphocytes to cross the blood–brain barrier and cause tissue damage [64, 65]. Therefore, less clear or compelling results with other drugs in terms of their final net impact on BV loss will be the result of a varying combination of both methodological issues, anti-inflammatory properties and neuroprotective effects; this might be the case of GA [55], dimethyl-fumarate (another drug with a possible neuroprotective effect [66]) which has shown positive results on BV loss only with the BID dose and teriflunomide (a drug without a known neuroprotective effect [67]) which has been demonstrated to reduce white matter volume loss only. Finally, we should keep in mind that global BV loss measures are not reflecting all real tissue damage occurring in MS patients, as they simply give us an estimate of a non-specific global effect that is the final net result of a number of pathogenic processes occurring in parallel in the brain (such as axonal degeneration, inflammation, new lesion formation, glial scarring, and others). Other, more pathologically specific, MRI techniques might be useful for that purpose once technical limitations have been overcome [68].

In summary, a number, but not all, of the available DMDs for treating RRMS patients have been demonstrated to reduce the rate of global BV loss in randomized clinical trials as well as in some open-label studies. Even though not only drug-specific, but also methodological aspects should be taken into consideration when interpreting treatment effects on BV; its well-proven relation to disability progression [69] makes accurate description of such effects very relevant in the definition of the therapeutic profiles of any drugs used in the treatment of MS.

Conflicts of interest Dr. Vidal-Jordana reports personal fees from Teva, Biogen-Idec, Novartis, and Genzyme, all outside the submitted work. Dr. Sastre-Garriga reports personal fees from Biogen-Idec, Novartis, Almirall, Teva, Roche, Merck-Serono and grants and personal fees from Genzyme, all outside the submitted work. Dr. Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the *American Journal of Neuroradiology* and *Neuroradiology*, has received speaker honoraria from Bayer, Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd., OLEA Medical, Stendhal, Novartis and Biogen Idec, receives research support from Bayer, and has research agreements with Siemens AG. Dr. Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen Idec, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi-Genzyme, Teva and Trophos.

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