Breakthrough Disease in Multiple Sclerosis – The Problem and Treatment Options

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Abstract

Early intervention with a disease-modifying therapy (DMT) is the most effective strategy for achieving disease control of relapsing–remitting multiple sclerosis (RRMS). However, current DMTs for RRMS are only partially effective in reducing disease activity, and approximately two-thirds of patients experience breakthrough disease. Breakthrough disease is characterised as an unacceptable degree of clinical or imaging evidence of disease activity, or progression, despite treatment. No validated definition of what constitutes unacceptable disease activity currently exists and identification of the condition remains challenging. Given the heterogeneous nature of MS, standard protocols will not be applicable to everyone. Management of breakthrough disease should be tailored to the individual, involving close monitoring of both clinical and magnetic resonance imaging parameters. Treatment options include increasing the dose, switching to another first-line therapy, escalation to a second-line therapy and the addition of other agents as combination therapy. There is a lack of evidence-based data to justify such approaches, but given the limited window of opportunity to derive the maximum benefit from DMTs, treatment modification where indicated is crucial. Various algorithms for the identification and treatment of breakthrough disease are discussed, and new and emerging therapies reviewed.

Keywords

Breakthrough disease, combination therapies, disease-modifying therapies, interferon, multiple sclerosis

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The disease-modifying therapies (DMTs) beta interferon (IFNβ) and glatiramer acetate (GA) were introduced in the 1990s for the treatment of multiple sclerosis (MS). Subsequent studies and clinical experience have shown that early intervention with a DMT provides the optimum chance of limiting the inflammatory process that contributes to irreversible axonal damage correlating with irreversible disability. However, DMTs cannot cure MS and are only partially effective. Furthermore, treatment response to DMTs is variable and unpredictable. In some patients, DMTs are sufficient to keep their disease process adequately controlled but in others, clinical or imaging evidence shows an unacceptable degree of disease activity or progression despite treatment. This is termed breakthrough disease.

A considerable body of clinical data indicates that early treatment of relapsing–remitting MS (RRMS) is crucial[1,2] and a clear window of opportunity exists to derive the maximum benefit from DMTs. Identification of breakthrough disease is therefore important to allow either a modification or a switch in treatment before the accumulation of irreversible disability.[3] To date, there is no evidence to guide changes in therapy in patients with breakthrough disease.[4] This article aims to describe and define breakthrough disease, to discuss its potential causes and to outline the optimum strategies to respond to breakthrough disease.

Definition of Breakthrough Disease

Breakthrough disease is characterised as an unacceptable degree of clinical or imaging evidence of disease activity or progression despite treatment. However, there is currently no validated definition of what constitutes unacceptable disease activity. Differentiating between what might be within the spectrum of DMT efficacy versus breakthrough disease remains challenging. In breakthrough disease, treatment efficacy that had been established over a period of time disappears, and there is further progression of disability, increased frequency or severity of relapses, increased magnetic resonance imaging (MRI) evidence of disease activity, and/or cognitive deterioration.

It is important to differentiate breakthrough disease from treatment failure. Following initiation of therapy, there are three possible outcomes. The optimum outcome is no disease

Table 1: Criteria for Identifying Breakthrough Disease

Parameters Used to Identify Breakthrough Disease			Reference
Relapses	EDSS	MRI Findings	
≥1 relapse after 3 months on therapy		≥2 Gd+ lesions in 3-monthly scans	33
Mean relapse rate >1 per year		<67 % reduction in Gd+ lesions per year	81
≥2 relapses with incomplete remission in previous 2 years	>1 point in 2 years		82
≥2 relapses	≥1.5 increase sustained over 6 weeks in past 1 year	Gd+ lesions on MRI in last 8 weeks	83
≥2 on-therapy relapses in 2 years	≥1 point in previous 2 years		84
1 relapse in last year while on IFNβ for ≥3 months	1 point in last year while on IFNβ for >6 months		85
≥2 on-therapy relapses in 1 year, or severe relapse (>2 points on functional system or >1.5 point increase in EDSS)			86
≥3 relapses in 6 months on therapy	Rapid accumulation of disability defined as ≥1 point over 6 months on therapy		87
≥1 relapse in 6 months on therapy		≥1 Gd+ lesion on screening MRI	88
≥2 on-therapy relapses in past year			89
≥1 documented on-therapy relapse in past year			90
≥1 on-therapy relapse in past 1 year			56
≥1 on-therapy relapse in past 6 months	≥1 point in past 6 months	Increase in Gd+ or T2 lesion number on spine or brain MRI in past 6 months	91
On-therapy ARR ≥2 and ≥1 relapse in past 60 days		≥1 Gd+ lesion	92
≥1 relapse in past year		≥1 Gd+ lesion in past year	93
≥1 relapse in past year		≥2 Gd+ lesions on ≥1 baseline scans	94
≥2 on-therapy relapses per year		Continued disease activity on MRI	95
≥1 relapse in past 6 months	3 months' confirmed disability progression in past 6 months	≥1 active MRI scans in past 3 months	39
≥ 1 relapse		≥ 1 lesion	53

ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; IFNβ = interferon beta; MRI = magnetic resonance imaging.

activity. The patient may be not responding to the therapy; this is termed treatment failure. The third outcome is that the patient may have an unacceptable degree of clinical disease activity despite showing some response to the treatment; this is breakthrough disease. The term 'suboptimal response' is often used in publications and is generally considered synonymous with breakthrough disease.

Potential causes for breakthrough disease include loss of sustained efficacy in long-term use, non-compliance, drug interactions and high titres of neutralising antibodies (NAbs). Poor compliance is a preventable cause of breakthrough disease and is affected by multiple issues including aversion to injections, side effects, frequency of administration, perceived efficacy, self-esteem, level of disability, treatment convenience, and the support provided by family and healthcare providers.

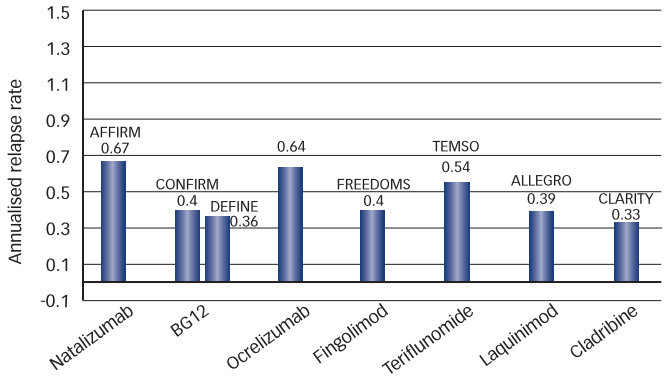
Estimates of the prevalence of breakthrough disease are hampered by differing interpretations of its definition. Data from clinical studies of IFNβ and GA and in the placebo arms of trials of newer therapies show that about two-thirds of patients with RRMS experience relapse or new lesions within two years of starting DMTs.[5–10] In a cohort of 252 patients treated with IFNβ, 20–50 % of patients experienced a marked increase in disability or a high number of relapses within a short period of time (<6 years) after the onset of treatment.[11] Analysis of the Prevention of Relapses and disability by Interferon Subcutaneously in MS 4-year (PRISMS-4) study, found that 39 % of patients receiving therapy experienced breakthrough (defined as any relapses or disease progression) after a year of treatment, and 89 % of these patients went on to develop further breakthrough in years 2–4.[12]

Identification of Breakthrough Disease

There is no established monitoring strategy to identify breakthrough disease although various algorithms have been proposed. Recent recommendations suggest assessing changes in relapse frequency and severity, progression of disability as measured by the Expanded Disability Status Scale (EDSS) and transition from a relapsing to progressive disease course.[13,14] A summary of criteria used to identify breakthrough disease in clinical studies is given in *Table 1*, and include clinical and MRI parameters. These criteria reflect the difficulty in identifying the condition and the necessity for an individualised approach. In some cases, one of these parameters was considered sufficient for a diagnosis of breakthrough disease; in others more than one was required. In one study, the definition of breakthrough disease and the decision to recommend a switch of therapies was made by each patient's neurologist.[15] Those most commonly employed include one or more on-therapy relapse in the last year and one or more new gadolinium (Gd)-enhancing lesion on MRI. Changes in disability as measured on the EDSS have been employed in a minority of studies.

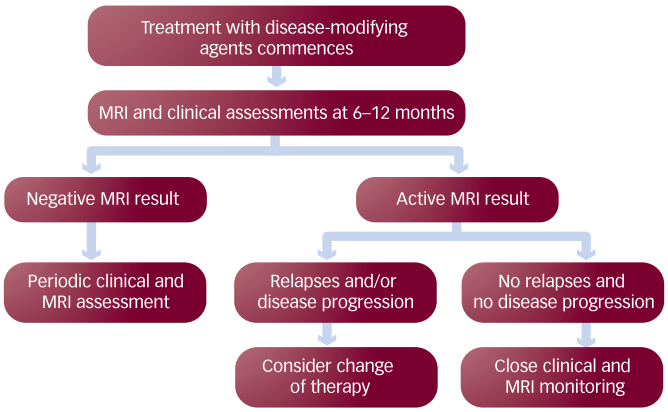
The Canadian MS Working Group attempted to characterise breakthrough disease by proposing Treatment Optimization Recommendations (TOR). The key questions addressed in the TOR were: how much activity is considered acceptable and when should treatment

Figure 1: Annualised Relapse Rate in Placebo-treated Patients Across Multiple Sclerosis Clinical Trials



Data sources: Fox et al., 2012,[10] Polman et al., 2006,[45] O'Connor et al., 2011,[74] Comi et al., 2012,[75] Gold et al., 2012,[76] Giovannoni et al., 2010,[77] Kappos et al., 2011[79] and Kappos et al, 2010.[104]

Figure 2: Proposed Algorithm for Evaluating Treatment Response in Patients with Relapsing–Remitting Multiple Sclerosis



MRI = magnetic resonance imaging. Source: Rio et al., 2009.[28]

be switched due to disease progression? The TOR were based on data obtained from natural history studies and clinical trials, and defined degrees of suboptimal response as a low, medium or high level of concern. The type or quality of relapse, disease progression or even MRI change could be of low-level concern, indicating a low chance of progression in the near term, and the patient can continue to receive their current therapy. If a medium-to-high level of concern is met, it means that there is a strong likelihood that this activity will translate into an earlier progression. In that case, it is important to consider changing to a therapy that may more effectively control disease activity.[16]

The International Working Group for Treatment Optimisation in MS recommended a change in therapeutic regimen following worrisome change in disease progression together with notable changes in relapse or MRI findings.[17] None of these recommendations have been prospectively validated; however, the Canadian TOR have characterised breakthrough disease in patients participating in the PRISMS-4 trial.[12,18]

Clinical Criteria

Clinical relapses are a useful measure of breakthrough disease as they have a sustained impact on disability. However, clinical measurements such as the EDSS do not provide a comprehensive assessment of disability; they are weighted towards changes in motor and ambulation, provide only a limited assessment of cognitive changes and do not take into account fatigue. Studies on the natural history of the course of RRMS suggest that the average frequency of relapses in the early stages is 0.5 to 1 a year in untreated disease.[19] A higher relapse rate may therefore be indicative of breakthrough disease.[20] One possible means of assessment of unacceptable disease activity is to use relapse rates observed in the placebo arms of clinical trials as the lowest acceptable level of MS clinical activity. *Figure 1* shows the placebo arm relapse rates in recent clinical trials of DMTs. If patients experience relapse rates at or above these levels, it is likely that their therapy is not effective and a switch of therapy may be warranted.

Magnetic Resonance Imaging Findings Indicative of Disease Activity

Subclinical disease activity detected using MRI plays an important role in monitoring disease activity in RRMS. Lesions seen on MRI and used to assess disease activity include hyperintense lesions on T2-weighted images, hypointense lesions on T1-weighted images and Gd-enhanced lesions on post-contrast images. Although MRI is currently the most sensitive tool for investigating MS, opinions differ on its use as a clinical outcome measure. It has been suggested that in patients experiencing clinically relevant relapses and disability, MRI may provide little additional information on disease activity or prediction of clinical outcome.[21] Conversely, another study has proposed that T2 lesion volume measured by MRI may predict increased risk of conversion from first isolated clinical demyelinating event to clinically definite MS, as well as disability progression over 20 years, especially if present early in the disease course.[22] MRI atrophy measures, particularly measurement of gray matter atrophy are also a useful measure of disease activity.[23–25] However, they are not currently used in the assessment of breakthrough disease as atrophy develops slowly and the rate of atrophy varies from year to year.

New MRI lesions can indicate breakthrough disease in a patient who is clinically stable. A meta-analysis suggested that the effect of a treatment in reducing relapses can be predicted by the reduction in active lesions observed by MRI.[26] MRI indicators of disease activity in cohort studies do not correlate strongly to relapses at the individual level. However, a number of studies have demonstrated a relationship between the development of new MRI lesions and a suboptimal clinical response. Patients receiving IFNβ with more than two new or enlarging T2 lesions after two years had significantly more clinical disease progression than in other subgroups.[27] A report discussing approaches to the management of breakthrough disease suggested that in a clinical setting, the counting of new MRI lesions is a more practical strategy than the measurement of lesion volume changes.[4] A proposed algorithm showing how MRI may be used to evaluate breakthrough disease is given in *Figure 2*.[28]

Biomarkers of Breakthrough Disease

To date, NAbs to IFNβ therapy has been identified as the only blood biomarker with the potential to reliably indicate treatment response.[29] High titres of NAb abolish the *in vivo* response to IFNβ.[30] It has been suggested that high NAb titres may be combined with MRI measurements during the first six months of IFNβ treatment to give added predictive value of breakthrough disease. In a study of 147 patients, those in whom these predictive factors were not seen, had a less than 10 % chance of developing breakthrough disease during the first two years of treatment.[29] However, in another study, patients

Table 2: Summary of Studies Evaluating the Efficacy of Switching Strategies in Patients with Breakthrough Disease

Therapy Switch	Study Design	Outcome	Reference
IFNβ to GA	Obs, n=32, 37.5 months	Mean ARR reduced from 1.32 to 0.52	90
IFNβ to GA IFNβ to different IFNβ GA to IFNβ	Obs, n=96, 6 years	Mean ARR 0.96 to 0.18 Mean ARR 0.36 to 0.16 Mean ARR 0.66 to 0.18	95
IFNβ to GA IFNβ to different IFNβ GA to IFNβ	Obs, n=114, 3 years	Median ARR 0.5 to 0.25 (p=0.92) Median ARR 0.5 to 0 (p=0.01) Median ARR 0.68 to 0 (p=0.02) Proportion of relapse-free patients increased in all groups	96
IFNβ to mitoxantrone (3 months) to IFNβ	Obs, n=10, 33 months	EDSS and relapse rate were stabilised and Gd+ lesions reduced in responders who continued IFNβ and nonresponders who resumed mitoxantrone therapy after 6 months of IFNβ	87
IFNβ to mitoxantrone	Obs, n=69, 1 year	Proportion relapse-free increased from 32 % to 92 % and proportion progression-free increased from 23 % to 70.5 % (p<0.0001 for both); proportion with new MRI activity decreased from 43 % to 15.8 %	84
IFNβ, GA, IVIG or MTX to CTX	Open-label, n=12, 15 months	5 patients decreased EDSS scores by 1.0 or more. 2 patients had a single Gd+ lesion at baseline; these lesions resolved after high-dose CTX treatment	89
IFNβ to mitoxantrone	Obs, n=12, 6 years	ARR reduced from 0.53 to 0.15	95
IFNβ/GA to NZ, immunosuppressants	Open-label, n=993	Relapse rate decreased by 70 % (p<0.001) in switchers to NZ and by 77 % (p<0.001) in switchers to immunosuppressants	15
IFNβ/GA to GA/IFNβ (SWI) or NZ (ESC)	Open-label, n=285, 24 months	At 12 months no differences in proportions of patients free from relapse, disability progression, MRI activity and combined activity. After 24 months more in the ESC than SWI group free from relapse (p<0.0001), disability progression (p=0.0045), MRI activity (p=0.0003) and combined activity (p<0.0001)	53
IFNβ to different IFNβ	Obs, n=4,754, 2 years	No benefit from switching	43

ARR = annualised relapse rate; CTX = cyclophosphamide; EDSS = Expanded Disability Status Scale; ESC = escalating; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; IFNβ = interferon beta; IVIG = intravenous immunoglobulin; MP = methylprednisolone; MTX = methotrexate; NZ = natalizumab; Obs = observational; PML = progressive multifocal leukoencephalopathy; SWI = switching.

with RRMS underwent monthly MRI scans to assess their response to IFNβ. No clear association between NAb profile and MRI response was evident.[31] In addition, a study of breakthrough disease during IFNβ treatment found no corresponding differences in biologic responsiveness to treatment in NAb-negative patients and concluded that the spontaneously occurring variation in underlying disease activity between patients causes the varying level of breakthrough disease observed in IFNβ-treated patients with MS.[32]

Persistent antibodies to natalizumab have been identified in a minority of patients (6 %) and appear between three and six months after therapy is initiated.[33] Antibodies to GA have also been identified but there is no evidence that these antibodies affect biological or clinical response.[34] Other assays of IFNβ efficacy include measuring the expression of IFN-induced GTP-binding protein (myxovirus resistance protein 1, Mx1) in response to IFNβ administration.[35,36] Many other biomarkers, including genetic markers have been investigated, but studies are still in the early stages and new biomarkers of breakthrough disease are unlikely to become available in the near future.

Strategies for Responding to Breakthrough Disease

After establishing that a change in treatment may be necessary when breakthrough disease is encountered during treatment with a DMT, several factors need to be considered in selecting the next treatment, including safety profile, monitoring requirements and patient lifestyle factors that might influence treatment compliance. Patients changing to a more progressive disease stage may be reaching the end of the window of opportunity for immunomodulatory treatment and may need to switch to more aggressive agents.[37] Three strategies may be considered: changing the dose, switching therapies or adding a therapy to the current regimen (combination therapy).

Dose Escalation Strategies

In clinical practice it has become routine practice to switch patients starting with low-dose to high-dose IFNβ in case of breakthrough disease, according to consensus group recommendations.[14,38] Data from two head-to-head studies comparing low and high dose IFNβ regimens suggested that initiation of treatment with high-dose IFNβ resulted in better outcomes than in those on low-dose regimens.[39,40] It has also been suggested that increasing the dose of IFNβ may reduce subclinical signs of disease activity in RRMS patients.[41] However, a recent observational post-marketing study (n=121) revealed that switching from the low-dose to high-dose IFNβ in cases of breakthrough disease did not reduce the risk of further relapses or increased disability.[42] After a 2-year follow-up, 60 % of patients had a relapse and 42 % had sustained progression on the EDSS score. Overall 70 % of the patients showed some clinical disease activity after the switch. It was noted, however, that patients who switched only on the basis of MRI activity (even in absence of clinical attacks) had a lower risk of further relapses (hazard ratio [HR]: 5.55, p=0.001). A high EDSS score (HR: 1.77, p<0.001) and the combination of clinical and MRI activity at switch raised the risk of sustained disability progression after increasing the IFNβ dose (HR: 2.14, p=0.01). The results may suggest that the majority of switchers were poor responders to IFNβ therapy, and a treatment regimen involving dose escalation of IFNβ may be useful only in selected cases.

Switching Strategies

Although switching among IFNβ, GA and natalizumab is common in clinical practice, there are no clinical trial data to guide these decisions.

Table 3: Summary of Studies Evaluating the Efficacy of Combination Strategies in Multiple Sclerosis

Combination	Study Design	Outcome	Reference
IFNβ + CTX	Open-label, n= 30, 24 months, prior IFNβ	The patients who had experienced a high number of relapses at baseline showed a significant improvement in yearly relapse rate at 12 months and a further improvement at 24 months (p<0.001) but no significant differences in EDSS score or T2 lesion load	86
IFNβ + CTX + MP	Randomised single-blind parallel group, n=59, 24 months, prior IFNβ	Combination therapy with CTX/MP and IFNβ decreased number of Gd+ lesions and slowed clinical activity	83
IFNβ + doxycycline	Open-label, n=15, 7 months, prior IFNβ	Combination resulted in reductions in Gd+ lesion number and EDSS values (p<0.001 for both)	92
IFNβ + mycophenolate mofetil	Phase II study, n=24, 12 months, treatment naïve	Combination showed no statistically significant improvement	97
IFNβ + mycophenolate mofetil	Pilot study, n=26, 12 months, treatment naïve	Combination showed no statistically significant improvement but evidence to support the need for a larger study	97,98
IFNβ + daclizumab	Open-label, n=11, 10.5 months, prior IFNβ	New and total Gd+ lesions reduced by 78 % (p=0.004) and 70 % (p=0.002), respectively	82
IFNβ + daclizumab	Open-label, n=9, 27.5 months, prior IFNβ	Reduction in total Gd+ lesion and new Gd+ lesions and relapses (p<0.001); EDSS, time ambulation and NRS were reduced (p<0.05)	94
IFNβ + MP (NORMIMS trial)	RCT, n=130, 96 weeks, prior IFNβ	Combination leads to a 62 % reduction in ARR (p=0.001) and 76 % probability of remaining relapse free versus 34 % placebo (p<0.001). A high proportion of patients withdrew from the study before week 96 (26 % on MP versus 17 % on placebo)	99
IFNβ + MP (MECOMBIN study)	RCT, n=341, 3–4 years, treatment naïve, IFNβ for 3 months before combination	Combined group had significant reduction in ARR and better MRI outcomes	100
IFNβ + azothioprine	Obs, n=85, 5 and 10 year data, prior IFNβ	Azathioprine add-on in patients with suboptimal response to IFNβ showed no improvement on the disease activity	101
IFNβ + azothioprine + corticosteroids (ASA trial)	RCT, n=181, 2 years, IFNβ naïve	Combined treatment regimen does not improve outcomes	102
IFNβ + simvastatin (SV)	Double-blind RCT, n=85, 12 months, prior IFNβ	The total relapse number in the SV group was significantly lower than placebo (p=0.01). EDSS lower in the SV group but not significant. Fewer Gd+ and new T2 lesions but not statistically significant	103
IFNβ + MTX/MP (ACT trial)	Placebo controlled RCT, n=313, 12 months, prior IFNβ	No significant benefits observed though a reduction in NAbs was noted with MP	93
IFNβ + NZ (SENTINEL trial)	Phase III RCT, n=1,171, 116 weeks, prior IFNβ	Combination showed 24 % reduction in disability progression (HR 0.76, p=0.02), lower ARR (0.34 versus 0.75, p<0.001) and fewer new or enlarging lesions on MRI (0.9 versus 5.4, p<0.001). 2 cases of PML in combined group	56
IFNβ + teriflunomide	Phase II trial, n=118, 24 weeks, prior IFNβ	Relative risk reductions (RRR) of T1 Gd+ lesion number 84.6 % (p=0.0005) and 82.8 % (p<0.0001) for addition of 7 and 14 mg teriflunomide at 48 weeks. T1 Gd+ lesion volume was reduced in the 7 mg group (RRR 72.1 %, p=0.1104) and 14 mg group (RRR 70.6 %, p=0.0154). Non-significant reduction in ARR	59
IFNβ + GA	Open-label, n=83, 24 months, prior GA or IFNβ	Outcomes for combined group similar to a first-line DMT responders group, higher psychological impact in the combined group	91
GA+ NZ (GLANCE trial)	Phase II trial, n=110, prior treatment with GA	New Gd+ or T2 hyperintense lesions 0.9 ± 2.1 with combination versus 2.6 ± 5.4 (p=0.057). Non-significant improvement in ARR in combination	57
DMT + rituximab	Phase II trial, n=30, 52 weeks, prior treatment with DMT and breakthrough disease	Gd+ lesions were reduced after treatment with rituximab, 74 % of post-treatment MRI scans being free of Gd+ activity versus with 26 % free of Gd+ activity at baseline (p<0.0001). 88 % reduction in median Gd+ lesions	58

ARR = annualised relapse rate; CTX = cyclophosphamide; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA= glatiramer acetate; Gd+ = gadolinium-enhancing; HR = hazard ratio; IFNβ = interferon beta; MP = methylprednisolone; MRI = magnetic resonance imaging; MTX = methotrexate; NAbs = neutralising antibodies; NRS = Neurologic Rating Scale; NZ = natalizumab; Obs = observational; PML = progressive multifocal leukoencephalopathy; RCT = randomised controlled trial.

Data on the effectiveness of switching strategies are scarce; a summary is given in *Table 2*. The large Quality Assessment in Multiple Sclerosis Therapy (QUASIMS) study (n=4,754) showed that switching between IFNβ regimens did not confer any significant benefits. All IFNβ products showed similar effectiveness and benefits were consistently superior when IFNβ was used as initial rather than follow-up therapy.[43]

In cases of breakthrough disease with a high level of concern, switching to natalizumab or mitoxantrone may be indicated although these drugs carry the risk of more serious adverse effects.[44–46] Natalizumab has been associated with a risk of progressive multifocal leukoencephalopathy (PML) due to reactivation of latent JC virus (JCV). Recently a two-step ELISA test to detect JCV antibodies (JCVAb) as a marker for prior exposure has been developed,[47] which has increased the utility of natalizumab. However, discontinuing natalizumab has been associated with an aggressive return of clinical disease activity.[48] A switch to fingolimod has been suggested to address this issue but isolated case reports suggest that fingolimod is insufficient to prevent such a return of disease activity.[49,50] However a clinical trial to investigate switching from natalizumab to fingolimod is ongoing.[51]

Switching from IFNβ or GA to fingolimod has been found to enhance efficacy with no unexpected safety concerns.[52]

Two recent studies have investigated the effect of switching to natalizumab in patients with breakthrough disease. In an open-label retrospective cohort study, the relapse rate decreased by 70 % ($p<0.001$) in switchers to natalizumab and by 77 % ($p<0.001$) in switchers to immunosuppressants. The relapse rate in non-switchers did not decrease (6 %, $p=0.87$).[15] Results of another study suggested that switching to natalizumab is more effective than switching to high-dose IFNβ or GA on clinical and MRI findings in patients with breakthrough disease; however, the escalation strategy was clearly more advantageous only after the first year of follow-up.[53]

Combination Regimens

For patients with breakthrough disease who do not have NAbs and are compliant with therapy, the addition of another drug may be indicated.[4] The ideal combination regimen comprises individual components with different mechanisms of action and independent therapeutic efficacy. No large-scale trials have confirmed the efficacy of combination therapies in MS. Many small studies have investigated combination regimens and some show significant benefits, however most subsequent larger trials of these combinations have yielded negative or conflicting results (see *Table 3*). Many small trials are subject to various biases including small sample sizes, imbalances in baseline characteristics and being underpowered to achieve statistical significance. A frequent shortcoming in design has been failure to include arms of each component of the combination as monotherapy.[54] Results of individual studies are summarised in *Table 3* and include studies of DMTs with corticosteroids and cytotoxic agents such as azothioprine, methotrexate, cyclophosphamide and mycophenolate mofetil. With the exception of mitoxantrone, these agents are approved for use in other diseases and are used off-label in the treatment of MS. Combinations of statins and IFNβ have also been investigated but a recent meta-analysis concluded that this combination yielded no significant benefit.[55]

Of the various combinations studied, there is sufficient evidence from those combining corticosteroids and IFNβ to warrant further study of this treatment regimen. The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) trial showed a clear advantage of natalizumab plus IFNβ over IFNβ alone on clinical and imaging endpoints.[56] However, the trial did not have a natalizumab monotherapy arm and it is therefore unclear whether the superior outcomes were a result of the combination or solely natalizumab. The Phase II Glatiramer Acetate and Natalizumab Combination Evaluation (GLANCE) trial showed an advantage of natalizumab plus GA over GA alone in terms of imaging but not clinical outcomes.[57] Other promising combinations of DMTs include rituximab as an add-on therapy to DMTs. A Phase II study found that this combination reduces Gd-enhancing brain lesions in breakthrough disease.[58] A recent study found that the combination of IFNβ and teriflunomide improves imaging outcomes.[59] Of the combinations of DMTs and cytotoxic drugs, the combination of IFNβ and cyclophosphamide has yielded the most encouraging results to date.

Several ongoing clinical trials may provide evidence to support combined treatment regimens in breakthrough disease. The Phase II Combination Study of BG-12 has recently completed,[60] as has the Phase II Cladribine Add-on to Interferon-beta Therapy in MS Subjects With Active Disease (ONWARD) trial.[61] The results of the CombiRx trial, a 3-year multicentre double-blind randomised study investigating the combination of GA and IFNβ, have recently been released and show that the combination was not superior to either agent alone.[62,63] A Phase II clinical trial to investigate the combination of ocrelizumab is currently ongoing.[64] Following observations that estriol may be used in the treatment of RRMS, a randomised controlled trial is underway to explore the combination of GA plus estriol.[65]

Despite encouraging data, the results and designs of studies of combination therapies to date are not robust enough to guide treatment decisions and need further confirmation by large, randomised controlled trials. Therefore, the usefulness of combination therapy in breakthrough disease currently remains uncertain.

Criteria for Selecting Treatment Strategies

Previously, expert panels of neurologists developed a treatment algorithm for the management of breakthrough disease.[66,67] In patients on IFNβ who were NAb-negative the addition of another therapeutic agent such as a pulse treatment schedule of corticosteroids (1 g/month or 1 g/day for 5 days every 4 months) was recommended followed by an oral steroid taper.[68] In prescribing long-term high-dose pulse corticosteroids, the physician should consider issues such as exacerbation of peptic ulcers, osteoporosis, diabetes and hypertension.[69] If breakthrough disease is sustained in NAb-negative patients, the next stage should be a switch to GA, elevation to natalizumab or combination therapy involving cytotoxic agents.

In 2009, the Neutralizing Antibodies to Interferon β in Multiple Sclerosis (NABINMS) consortium issued the following recommendations for patients on IFNβ. In patients who show a positive clinical response, are Nab-negative and/or have demonstrable Mx1 biological activity, IFNβ therapy should be continued. In patients with confirmed high titres of NAbs and/or lack of Mx1 biological activity, a switch to an alternative DMT is recommended. In patients with intermediate disease activity, continuation of IFNβ therapy could be considered in NAb-negative patients, whereas high titres of NAbs or a lack of Mx1 biological activity warrant consideration of a different treatment. In patients with high disease activity, a different treatment regimen should be initiated, regardless of the results of NAb or Mx1 biological activity testing.[36]

In a recent study, patients who experienced a relapse while on GA were divided into two groups: those who changed to any other treatment and those who did not. There was no significant difference in subsequent annualised relapse rate (ARR) and time to next relapse. In addition, no significant difference in time to sustained progression on the EDSS was observed. This suggests that a single relapse may not be sufficient to warrant switching therapies.[70]

There are few studies investigating the management of breakthrough disease in routine clinical practice. In a study of paediatric MS patients, following diagnosis of breakthrough disease, over half (56 %) continued receiving monotherapy, while 25 %, 11 %, and 8 % received 2, 3, or 4 or more sequential therapies, respectively, during a mean 3.9 years. In the majority of cases (79 %), the second-line DMT was restricted to IFNβ and GA. In the remainder, cytotoxic agents (cyclophosphamide, mitoxantrone), natalizumab, corticosteroids and daclizumab were used. Hispanic children were more likely to experience breakthrough disease while receiving first-line DMTs than non-Hispanic children.[71]

Future Trends and Developments in Multiple Sclerosis Treatment

In recent years, many therapeutic agents have been developed that could potentially play a valuable role in the treatment of breakthrough disease. In particular, attention has focussed on oral therapies because of their ease of administration.[72] In 2010, fingolimod, a sphingosine 1-phosphate receptor modulator, became the first oral therapy to be approved in the treatment of MS following a Phase III study in which it reduced ARR compared to IFNβ-1a.[52] A recent report has recommended that it is considered alongside mitoxantrone and natalizumab as second-line therapy in cases of breakthrough disease.[73] The most recently approved DMT is terifunomide, another oral medication that acts by inhibiting pyrimidine synthesis, which received US Food and Drug Administration (FDA) approval in September 2012 following the results of an earlier Phase III trial.[74] Other oral therapies awaiting approval include laquinimod[75] and BG-12.[10,76] Cladribine has also demonstrated efficacy in clinical trials.[77]

Monoclonal antibodies undergoing the approval process include alemtuzumab. A recent Phase III clinical trial showed that in cases of breakthrough disease, alemtuzumab reduced relapse rates and sustained accumulation of disability.[8] Recent success in other immune-mediated diseases, such as rheumatoid arthritis, has drawn attention to B-cell-directed therapies as a treatment for MS. Rituximab is a monoclonal antibody that targets CD20, is exclusively expressed on pre-B and mature B cells.[78] Other B-cell targeted monoclonal antibodies in development include ocrelizumab[79] and ofatumumab.[80]

In summary, new and improved disease modifying drugs and therapeutic strategies that could impact treatment choices for MS patients with breakthrough disease are becoming available. The varying modes of action of these new therapies offer a wide spectrum of efficacy and safety and have elevated the treatment goals for patients with MS. Freedom from disease, defined by the absence of relapses, disability progression, and MRI evidence of disease activity, is increasingly seen as the measure of treatment success.

Summary and Concluding Remarks

Although the heterogeneity of RRMS precludes a strict treatment algorithm, there is a need for a common approach to the identification and management of breakthrough disease. There is a requirement for validated assessment and treatment protocols as well as validated markers to treatment response. Patients should be carefully monitored using both MRI and clinical parameters for an adequate response to therapy. Decisions about changes to treatment regimens should involve both physician and patient and take into account the timing of therapy as well as individual patient factors. Although there is a lack of evidence-based data justifying changes in treatment regimens, there is a clear need for physicians to act when breakthrough disease is identified. A change in therapy may involve an increased dose, switching to a different DMT or a combination therapy. Early identification and management of breakthrough disease improves the chances of disease control before the onset of irreversible disease progression and disability. ■

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