Improving Patient Satisfaction with Injection Devices in Multiple Sclerosis Improves Adherence

Karl Baum

Chief of Neurology, Hennigsdorf Hospital

DOI:10.17925/ENR.2009.04.02.64

Abstract

Various studies have demonstrated that regular injections of interferon beta (IFN-β), whether subcutaneously or intramuscular, are effective as maintenance therapy in multiple sclerosis (MS), with acceptable safety and tolerability profiles. While tolerability and adverse events are reported to be comparable across the three most commonly available formulations of IFN-β (Betaferon®, Bayer Schering Pharma; Rebif®, Merck Serono; and Avonex®, Biogen Idec), the formulation of IFN, needle diameter and injection method have been implicated in the rate of injection-site reactions (ISRs) and injection-site pain (ISP), which can ultimately affect a patient's adherence to therapy. Providing MS patients with information and education regarding their condition and available treatments is considered to be of high importance among patients, and the availability and support of specialist MS nurses, or even an educational website, has been associated with improved quality of life among MS patients. Recent data from European surveys of patients and nurses show consistently high satisfaction with a new Betaferon auto-injection system, which offers automatic withdrawal of the needle, reduced needle size and variable depth adjustment. IFN formulation, nursing support and use of an auto-injector can therefore have a major impact on adherence to therapy.

Keywords

Multiple sclerosis, interferon-β, safety, tolerability, injection-site reactions, injection-site pain, auto-injectors

Disclosure: Karl Baum has received lecturing honoraria from Bayer Schering, Biogen idec, Merck-Serono, TEVA/sanofi-aventis and Novartis, and is a consultant for Bayer Schering.
Received: 11 December 2009 **Accepted:** 26 February 2010
Correspondence: Karl Baum, Department of Neurology (MS Centre), Klinik Hennigsdorf, Marwitzer Straße 91, Hennigsdorf, 16761, Germany. E: kb.hennigsdorf@gmx.net

Interferon beta (IFN-β) is now established as an effective maintenance therapy for multiple sclerosis (MS) that can both slow disease progression and reduce clinical exacerbations.[1–6] Studies have demonstrated that the three widely used IFN-βa formulations – IFN-β1b 250µg (8MIU) by subcutaneous (SC) injection every other day (EOD; Betaferon®, Bayer Schering Pharma); IFN-β1a 44µg (12MIU) by SC injection three times per week (Rebif®, Merck Serono); and IFN-β1a 30µg (6MIU) by intramuscular (IM) injection once per week (Avonex®, Biogen Idec) – all offer acceptable tolerability and safety profiles.[7,8] Data suggest that the two higher-dose, more frequent formulations (Betaferon and Rebif) offer better efficacy than the lower-dose, less frequent Avonex.[7–9] Adverse events (AEs) are reported to be similar across all three formulations.[7,8] However, according to one comparative study there may be an increase in headaches and injection-site reactions (ISRs) with higher-dose SC formulations compared with lower-dose IM IFN-β.[7] However, this study pre-dated the development of new SC injector technology that is likely to influence ISRs. Injection-site pain (ISP) and ISRs are a common concern with injectable therapies and can impair adherence to treatment and potentially contribute to discontinuation of therapy.[7,8,10] This article reviews evidence on factors influencing ISRs, ISP and adherence, and presents the results of patient and nurse surveys on a new IFN-β auto-injector.

Impact of Injection-site Pain and Reactions

The growing recognition of the importance of ISP and ISRs has fuelled research into drug formulations and mechanisms of administration. Although a number of orally administered drugs are in development for the treatment of MS, none is currently approved, thus continued research into minimising the ISP and ISRs associated with IFN-β could improve adherence to the therapies that are widely used today. The use of auto-injectors has been shown to be one approach that can reduce ISRs. Auto-injectors were linked with significantly lower rates of ISRs in over 1,800 patients with relapsing–remitting MS (RRMS) receiving IFN-β over three weeks (79% versus 85% with physician-assessed ISRs and 66% versus 72% with patient-reported ISRs; $p<0.001$ for both comparisons).[11] An earlier report suggested that auto-injectors could reduce ISRs by close to 60% compared with manual injection.[12] Interestingly, in the pivotal IFN-β1b trial, which utilised manual injections, 69% of patients in the active treatment group reported at least one ISR compared with 6% of those receiving placebo.[13] By contrast, the more recent BENEFIT trial, in which IFN-β1b was predominantly administered by auto-injector, the reported ISR rate was 48% versus 8.5% with placebo.[14]

Other factors that could affect ISRs and ISP include the formulation of IFN and needle diameter. Low-dose and reduced frequency of administration of IFN-β1a may offer fewer ISRs and less ISP than either high-frequency IFN-β formulation, but data suggest that the efficacy of low-frequency IFN-β1a is significantly lower than that of the alternative formulations.[7–9] Therefore, a balance between efficacy and tolerability must be achieved. Evidence is now emerging that there are also differences in terms of ISRs and ISP between the two

high-frequency IFN-β formulations, in addition to the benefits of reducing needle thickness.[15,16]

The BRIGHT Study

The BRIGHT study was the first large-scale comparison of ISRs and ISP in patients with RRMS using 250µg IFN-β1b EOD versus 44µg IFN-β1a (2004/2005 formulation of Rebif) three times a week. Patients enrolled into the study had been previously treated with IFN-β for at least one month but not more than three months and had completed the dose-titration phase of their treatment.[15]

Within the study observation time of four to five weeks, patients injected 15 consecutive doses of their prescribed IFN formulation and rated their ISP on a visual analogue scale (VAS) immediately, 30 minutes and 60 minutes after each injection. The main study outcome was the proportion of patients who were pain-free at all three time-points after each injection. The study nurse telephoned patients each week to check for AEs, wellbeing and correct VAS diary. At the end of the study, patients assessed the impact of pain on overall treatment satisfaction and ease of auto-injector use (where applicable). The study nurse assessed ISR occurrence and severity at both the beginning and the end of the study. Other end-of-study measures included disease status, AEs and concomitant medication.

A total of 454 patients (306 on Betaferon and 148 on Rebif) entered the study at 76 centres in 13 countries. Reported outcomes were based on the valid case (VC) population of 445 patients (303 on Betaferon and 142 on Rebif), which excluded patients who either used a reduced IFN-β dose at least once or completed their VAS diary incorrectly. Baseline demographics and MS duration, status and disease characteristics were broadly similar in the two treatment groups.

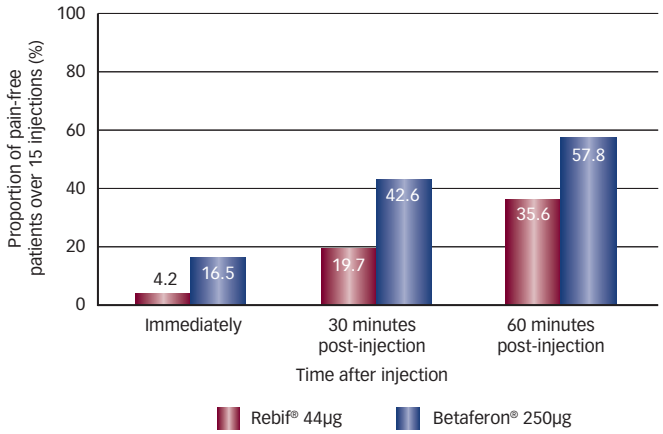
There were significantly higher proportions of pain-free patients and pain-free injections per patient at all time-points on Betaferon than on Rebif (p<0.0001) (see *Figures 1* and *2*). Similarly, mean VAS scores were lower (p<0.0001) for patients using Betaferon compared with Rebif at all time-points and across all injections. ISRs were also significantly more common in the Rebif group than in the Betaferon group (p=0.0184 and p<0.001 at visits 1 and 2, respectively).

It is reasonable to predict that reducing pain and ISRs would encourage patient adherence. This is consistent with the result that significantly more patients who injected Rebif than who received Betaferon reported that pain had negatively affected their satisfaction with treatment (p=0.006). A smaller needle gauge is also likely to promote adherence; this study was not powered to detect a difference in pain according to needle size, but did show a non-significant trend for fewer pain-free injections with a smaller-diameter needle. In a *post hoc* sub-analysis, more patients were pain-free using the thinner 30-gauge needle at the 60 minutes post-injection time-point over all 15 injections (75.0% versus 52.2% with the 27-gauge needle; p=0.0086).[17]

The REFORM Study

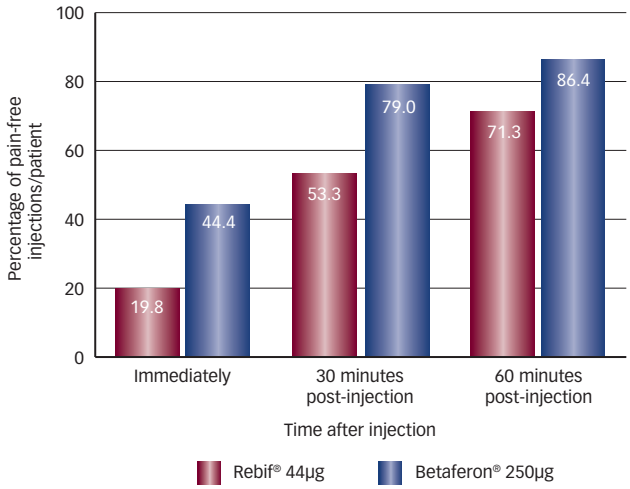
More recent data on the comparative tolerability of IFN-β1a and IFN-β1b are available from the REFORM study,[18] which was a multi-centre, randomised, open-label comparison of the two treatments over 12 weeks. Two groups of treatment-naïve patients with RRMS who were balanced for baseline demographic and disease parameters received either IFN-β1a 44ug SC three times weekly (n=65) or IFN-β1b 250ug SC every other day (n=64).

Figure 1: Mean Proportion of Patients Pain-free at 0, 30 and 60 Minutes After Injection in the BRIGHT Study



A significantly higher percentage of patients were pain-free on Betaferon than on Rebif at all time-points (p<0.0001). Source: Baum et al., 2007.[15]

Figure 2: Mean Proportion of Pain-free Injections per Patient After 0, 30 and 60 Minutes



A significantly higher mean percentage of patients had pain-free injections on Betaferon than on Rebif at all time-points (p<0.0001). Source: Baum et al., 2007.[15]

In this study, compliance was high on both treatments. For the primary end-point – mean change in patient-reported pain score on the visual analogue scale (VAS) from pre-injection to 30 minutes post-injection over the first 21 full-dose injections – there was no significant difference between IFN-β1a- and IFN-β1b-treated patients (p=0.425, 0.839 and 0.522 for immediately, 10 minutes and 30 minutes post-injection, respectively). The proportion of patients not taking analgesics and pain-free 60 minutes post-injection was slightly greater in the IFN-β1a group (p=0.039) during the titration period. There was a higher frequency of ISR with IFN-β1a compared with IFN-β1b (29.2 and 14.1%, respectively), but the rates of ISP were similar in both groups (6.2 and 6.3%, respectively). The indicence of adverse events was mostly similar for the two groups, and within the ranges and of the types expected for these medications. However, the incidence of increased alanine aminotransferase (ALT), nausea, urinary tract infection, increased serum ferritin, chills, influenza, injection-site bruising and abnormal liver function tests (LFT) were higher with IFN-β1a than with IFN-β1b. The REFORM study therefore showed essential similarity in the tolerability profiles of Rebif new

Table 1: Patient Feedback on Needle Gauge and Injection Pain Using the New Betaject System (Comfort)

	Italy (n=116)	Spain (n=112)	Pooled Results (n=228)
Consider new injection system less painful; n (% of respondents)	70 (60)	92 (82)	162 (71)
Feel a difference with the thinner (30G) needle; n (% of respondents)	71 (61)	85 (76)	156 (68)
The difference with the thinner needle is less pain; n (% of respondents who felt a difference)	55 (77)	77 (90)	132 (85)

formulation and Betaferon; an extension to the study will show whether there are any long-term advantages of either treatment in terms of tolerability.

The Evolving Role of the Nurse in Multiple Sclerosis

Regular nursing support is a key element in MS management. The role of the specialist MS nurse has grown with the increasing complexity of treatment; the widespread introduction of INF-β as a disease-modifying therapy has contributed to this expanding role.[19,20] According to a recently published survey, patients with MS consider information and education about MS and its treatment to be especially important elements of their nursing care.[21] Specialist MS nurses were nominated most often by patients as the appropriate care provider overall for specific needs, such as information about MS, general health education and advice about medication, relapse management and side effects of drugs. In the same survey, healthcare professionals also rated specialist nurses as the appropriate care provider for more than two-thirds of a list of 48 care needs. However, the authors stressed the continuing importance of non-specialist nursing care in MS management. The impact of various support elements on patient quality of life (QoL) was evaluated in the longitudinal, observational, 24-month BetaPlus study in patients with RRMS or secondary progressive MS. Data over a 12-month period showed that use of a specialist nurse programme or a patient education website resulted in the most pronounced increase in patient QoL during the analysed time-frame.[22]

Recent data from the BENEFIT trial may have important implications for nursing care in MS.[14,23,24] This study revealed reductions in MS progression when patients received 250µg Betaferon EOD after their first clinical demyelinating event, with a 50% risk reduction for progression to clinically definite MS (CDMS) after two years on Betaferon compared with placebo or delayed treatment.[14] At three- and five-year active-treatment follow-up, early Betaferon treatment was linked with a 41 and 37% reduction, respectively, in the risk of progression to CDMS compared with delayed Betaferon treatment.[22,23] Earlier placebo-controlled studies using various treatments and dosing schedules have also shown the value of early immuno-modulatory treatment in delaying conversion to CDMS.[14,25–27]

What does this mean for nursing care in MS? The results support early treatment with IFN-β. Increased prescribing in early MS could add a growing population of relatively well patients to the nurse's caseload. Supporting adherence to treatment in early MS or in patients with a first event suggestive of MS may represent a particular challenge with these patients.

Promoting Patient Adherence

Adherence is crucial to optimise treatment efficacy and hence patient outcomes. Studies in other chronic diseases have reported non-adherence rates of up to 80%, and have highlighted the impact of non-adherence on patient outcomes.[28–31] Key reasons for non-adherence or discontinuation of IFN in MS include perceived lack of efficacy (contributing to around 30–52% of discontinuations) and AEs (about 22% of withdrawals in a study of IFN-β and glatiramer acetate).[32,33] A high proportion of patients will experience ISP or ISRs at some point during their course of therapy; efficacy and comparative studies alike have previously reported frequencies of up to 85% with Rebif,[3,34] and 33% with Avonex,[34] although evidence suggests that dosage and injection methods may affect frequency of ISRs as well.[7] As mentioned earlier, injection methods have also been shown to result in varying frequency of ISRs with Betaferon.[13,17,24,35] Although the frequency of ISRs decreases over time, ISRs may be accountable for 12% of discontinuations from IFN-β treatment.[33] Injection anxiety can also be an important factor in determining whether a patient adheres to IFN-β therapy.[36]

There are two approaches that can promote adherence to IFN-β by addressing these factors: first, improving therapeutic support and patient education, and second, increasing treatment acceptability by minimising AEs, pain, ISRs and difficulty with self-injection.

Therapeutic Support and Patient Education

Manufacturers of injectable disease-modifying therapies for MS sponsor patient assistance programmes that offer education and mentor support. These are BETA Nurse (as part of BETAPLUS™; Bayer Schering Pharma/Bayer Healthcare), Avonex Services (Biogen Idec), MS Lifelines (EMD Serono/Pfizer) and Shared Solutions, MS Watch (Teva Neuroscience). Nursing support is integral to all of these programmes, although only BETA Nurse is 100% nurse-co-ordinated.[19] This type of programme can be particularly valuable in managing patient expectations of therapy through education, thus reducing the likelihood of stopping treatment for perceived lack of efficacy or AEs, as well as minimising ISP and ISRs through training and support.

As of 2004, the BETA Nurse programme had recruited over 10,000 patients, and only 1.6% had been lost to follow-up.[37] Support and advice on simple techniques, such as starting Betaferon on a reduced dose and gradually increasing to the full dose, using an auto-injector, rotating injection sites and using concomitant treatment such as ibuprofen or paracetamol as prescribed to reduce influenza-like symptoms, have been linked with excellent adherence. Only 0.8% of patients discontinued due to ISRs, 2.1% due to influenza-like symptoms and 1.7% for perceived lack of efficacy.

Treatment Acceptability

The BENEFIT study incorporated several measures to optimise treatment acceptability, consistent with the advice patients receive on the BETA Nurse programme.[14,37] Participants used auto-injector devices (if approved in their country) to reduce ISRs, and received paracetamol or ibuprofen to minimise influenza-like symptoms during the first three months of treatment.[14] The dose was also titrated from an initial 62.5µg, increasing by 62.5µg every fourth injection up to the full 250µg dose. Over 97% of patients in both the Betaferon and placebo groups received at least 80% of scheduled doses, and 96% of both groups chose to receive Betaferon in the extension study.

Table 2: Specialist Multiple Sclerosis Nurse Feedback on Their Satisfaction with Specific Design Features of the Betaject Comfort System (UK data, total n=48)

Design Feature	Satisfaction (weighted mean score)		
	-2	0	2
	Totally dissatisfied	Neither/nor	Totally satisfied
Ease of holding			+1.1
Ease of firing			+1.4
Withdrawal of needle			+1.6
Noise indicating end of injection			+1.6
Quiet operation			+1.1
Ease of loading			+1.0

Table 3: Specialist Multiple Sclerosis Nurse Feedback on Improvements of Specific Design Features of the Betaject Comfort System Compared with Older Betaject Models (UK data, total n=48)

Design Feature	Satisfaction (weighted mean score)		
	-2	0	2
	Totally dissatisfied	Neither/nor	Totally satisfied
Ease of holding			+1.1
Ease of firing			+1.4
Withdrawal of needle			+1.2
Noise indicating end of injection			+1.5
Quiet operation			+1.1
Ease of loading			+0.9

A further study, BEACON, is currently recruiting patients.[38] This study will address the impact of various factors on adherence to Betaferon therapy, focusing on the role of MS nurse support.

Impact of New Auto-injector Technology on Treatment Acceptability

Reducing ISP and ISRs is an important target for optimising treatment acceptability and hence adherence. While studies have shown the available IFN-βs to be similar in terms of tolerability and AEs,[7,38] the rate of ISRs is more variable depending on the IFN (e.g. 37% with Betaferon versus 8% with Avonex and 85% with Rebif versus 33% with Avonex).[7,33] One study suggests that ISRs may contribute to 12% of IFN-β discontinuations.[33,39–41] Previous studies have shown that using auto-injectors can improve treatment acceptability compared with manual injection.[11,12] New data comparing different new Betaferon auto-injectors are now available from four European surveys (in the UK, France, Italy and Spain). Patients with MS (in France, Italy and Spain) and specialist MS nurses (in the UK) returned consistently positive feedback on a range of attributes of the new Betaferon injection system, Betaject® Comfort, which offers a unique injection technology with automatic withdrawal of the needle. It offers a flexible depth adjustment (8mm/10mm/ 12mm) as well as injections with a reduced needle size (27–30G). In addition, a hidden needle system can help to overcome needle phobia, and an audible signal indicates when the injector can be safely withdrawn.[42]

Most patients in Italy and Spain (71%) rated Betaject Comfort as less painful than previous injection systems (see *Table 1*), while 94% of French respondents were either 'satisfied' or 'very satisfied' with the level of pain induced by Betaject Comfort. Interestingly, more than two-thirds of Italian and Spanish patients (68%) said that they could feel a difference using the new, thinner needle, of whom 85% described this difference as reduced pain compared with their older injection systems (see *Table 1*). Patients also linked the new auto-injector with reduced ISRs: 70% of Spanish respondents said that they experienced fewer ISRs with the thinner needle, and in Italy 46% of patients thought (based on personal experience) that the new injection system would cause fewer ISRs than previous systems (46% commented that they did not have any ISRs). Over one-third of Italian respondents (35%) said that the new system encouraged better adherence than previous injection systems.[42]

Having an invisible needle was viewed positively by about 90% and 81% of French and Italian respondents, respectively. The needle withdrawal system was also popular with patients: 89% of Spanish and 100% of both Italian and French respondents rated it as satisfactory or better.[42]

In the Italian survey, 69% of patients considered the new system to be more practical than previous systems. Practical benefits included ease of use, ease of remembering operating steps, reliability, comfort, practicality and speed of preparation ('easier' or 'much easier' to use: 62%; 'easier' or 'much easier' to remember steps: 59%; 'more reliable' or 'much more reliable': 59%; 'more comfortable' or 'much more comfortable': 74%; 'more practical' or 'much more practical': 88%; 'faster' or 'much faster' to prepare: 56%). Most patients also said that the new adaptor was more comfortable, simpler and more manageable than previous systems (88, 80 and 65%, respectively).

Most Spanish respondents (82%) rated the Betaject Comfort easier to access and inject different parts of the body, which may encourage injection-site rotation. The Spanish survey also found that patients rated the new pre-attached needle more (40%) or much more convenient (30%), while 79% reported that the pre-attached needle simplified the process.[42]

Global satisfaction with the Betaject Comfort was high, with 75% of Italian patients responding 'I like it' (60%) or 'I like it a lot' (15%), 71% of Spanish respondents being either 'quite satisfied' or 'very satisfied' and 100% of French patients being either 'satisfied' or 'very satisfied'.[42]

A sample including 20–25% of all specialist MS nurses in the UK (n=48) returned similar comments on the Betaject Comfort. Satisfaction was also high with the two most important features of an auto-injector (according to respondents; see *Table 2*), ease of holding and ease of firing (about 89 and 93%, respectively). About 90% or more of nurses considered the Betaject Comfort to be an improvement over previous models in terms of ease of holding and firing (see *Table 3*), with 94% of the nurses agreeing that, overall, the Betaject Comfort was an improvement over older Betaject models. These results correlate well with feedback from French patients with MS, over 80% of whom were satisfied or very satisfied with the Betaject Comfort's ease of handling. Similarly, needle withdrawal was highly rated by patients and ranked as the third most important feature by MS nurses.[42]

Over 70% of nurses were 'totally satisfied' and nearly 20% were 'satisfied' with the Betaject Comfort's hidden needle, which also gained positive feedback from 80–90% of patients. Nurses also commented that the new system was good for needle phobia and for hard-to-reach areas, and that it reduced bruising. These factors are all likely to promote adherence; indeed, several of the nurses surveyed volunteered the comment that the Betaject Comfort 'improves adherence'.[42]

Summary and Conclusions

Recent data suggest that adherence to a programme of IFN-β from the first demyelinating event can delay progression to CDMS and reduce relapses in MS. The tolerability and safety profiles of all three widely used formulations are generally good. Variations in efficacy and tolerability appear to be related to dose, formulation and mode of delivery.

Adherence is a major concern even with oral therapies, and injectable treatments such as IFN-β carry their own issues, notably ISRs, ISP and injection anxiety. Strategies that improve treatment acceptability and/or patient support are likely to promote good adherence and thus optimise treatment efficacy. These include:

- considering patient type when selecting an appropriate IFN-β;
- using an auto-injector whenever possible – this reduces pain compared with manual injection, and features such as a hidden needle may help alleviate injection anxiety; and
- ensuring that all patients with MS receive regular nursing support, to include education (including realistic efficacy expectations) and injection training, not only at the beginning of therapy but also throughout life.

New injection technologies such as the Betaject Comfort offer improved ease of use and reduced pain and ISRs compared with earlier auto-injectors. Surveys in four European countries indicate that both MS nurses and patients rate the Betaject Comfort system as an improvement over previous models that may enhance adherence.

In conclusion, it seems that a dual approach of optimising treatment acceptability through formulation and injector design and providing ongoing patient education and nursing support can increase adherence to injectable therapies, in both MS and other chronic conditions. ■

Karl Baum is Chief of Staff at the Neurological Clinic and Head of the Multiple Sclerosis Centre at Hennigsdorf Hospital, an academic teaching hospital of the Charité University of Berlin. His primary research and clinical interest is in multiple sclerosis (MS). He has extensive experience with immunomodulatory therapy for MS and has been the principal investigator for many studies in this area.

1. European Study Group on interferon beta-1b in secondary progressive MS, *Lancet*, 1998;352:1491–7.
2. The IFNB Multiple Sclerosis Study Group, *Neurology*, 1993;43:655–61.
3. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group, *Lancet*, 1998;352:1498–1504.
4. Jacobs LD, et al., *Ann Neurol*, 1996;39:285–94.
5. Li DK, Paty DW, *Ann Neurol*, 1999;46:197–206.
6. Paty DW, Li DK, *Neurology*, 1993;43:662–7.
7. Durelli L, et al., *Lancet*, 2002;359:1453–60.
8. Schwid SR, et al., *Arch Neurol*, 2005;62:785–92.
9. Barbero P, et al., *Mult Scler*, 2006;12:72–6.
10. Turner AP, et al., *Rehabil Psychol*, 2009;54:116–21.
11. Mikol D, et al., *Mult Scler*, 2005;11:585–91.
12. Tornatore C, Bartlett D, *J Neurol*, 2002;249(Suppl. 1):205, P814.
13. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group, *Neurology*, 1995;45:1277–85.
14. Kappos L, et al., *Neurology*, 2006;67:1242–9.
15. Baum K, et al., *Mult Scler*, 2007;13:1153–60.
16. Harris C, et al., *Int J MS Care*, 2005/2006;7:132–6.
17. Baum K, et al., *Mult Scler*, 2006;12(Suppl. 1):S197, P692.
18. Singer B, Jeffery D, Kirzinger S, et al., Presented at the 19th World Congress of Neurology, Bangkok, Thailand, 24–30 October 2009, poster PO10-TU-32.
19. Halper J, *N Neurosci Nursing*, 2009;41:E1–13.
20. www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf (accessed October 2009).
21. While A, et al., *J Clin Nurs*, 2009;18:2635–48.
22. Pozzilli C, et al., *J Neurol*, 2009;255(Suppl. 2):S614, P465.
23. Kappos L, et al., *Lancet*, 2007;370:389–97.
24. Kappos L, et al., *Lancet Neurol*, 2009;8:987–97.
25. Jacobs LD, et al., *N Engl J Med*, 2000;343:898–904.
26. Comi G, et al., *Lancet*, 2001;357:1576–82.
27. Comi G, et al., *Lancet*, 2009;374:1503–11.
28. Claxton AJ, et al., *Clin Ther*, 2001;23:1296–1310.
29. Ho PM, et al., *Arch Intern Med*, 2006;166:1836–41.
30. Lugaresi A, *Expert Opin Drug Deliv*, 2009;6:995–1002.
31. www.who.int/chp/knowledge/publications/adherence_full_report.pdf (accessed October 2009).
32. Rio J, et al., *Mult Scler*, 2005;11:306–9.
33. Tremlett HL, Oger J, *Neurology*, 2003;61:551–4.
34. Panitch H, et al., *J Neurol Sci*, 2005;239:67–74.
35. O'Connor P, et al., *Lancet Neurol*, 2009;8:889–97
36. Mohr DC, et al., *Ann Behav Med*, 2001;23:125–32.
37. Schapiro RT, Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting, 2004; poster S04.
38. clinicaltrials.gov/ct2/show/NCT00787657 (accessed October 2009).
39. Betaferon, Summary of Product Characteristics, Bayer Schering Pharma, last reviewed February 2009.
40. Extavia 250 microgram/ml powder and solvent for solution for injection, Summary of Product Characteristics, Novartis, UK, last reviewed March 2009.
41. Rebif solution for injection in pre-filled syringes, Summary of Product Characteristics, Merck Serono, UK, last reviewed October 2009.
42. Data on file, Bayer Schering Pharma AG