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Interferons and Natalizumab for Multiple Sclerosis

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Health policy background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. It is the disease which in young adults most frequently leads to lasting disability. Estimates suggest that between 67,000 and 138,000 people in Germany are affected. The costs of the disease are considerable, in particular due to the need for both professional and informal long-term care and high indirect costs. Premature retirement after 13 years of disease is observed in around 40% of patients. Patients and/or their families (or other informal helpers) assume around two thirds of the costs. Widespread use of interferons is expected to raise the overall costs of MS care.
Therapeutic options for treating MS are subdivided in medication for modifying (i. e. slowing) the course of the disease and in symptomatic therapy. Treatment with recombinant interferons is one option of a disease modifying treatment. Beta-interferons have been licensed for treatment of MS in Germany since 1995. The therapy with interferons however puts a high financial strain on the health system and it is questionable to what extent the effectiveness of the treatment which is hard to predict will offset the high costs. Recent studies also examine the disease-modifying efficacy of natalizumab, a monoclonal antibody. After two cases of progressive multifocal leucoencephalopathy, one of which was fatal, there have been concerns about the safety of the drug despite promising clinical study results in the USA. As a consequence, natalizumab has transiently been taken off the market since February 2005. However, after the publication of a further study natalizumab has had its licence renewed in the USA and Germany with special requirements. Natalizumab is used by failure of interferon therapy.
The current HTA report focuses on the assessment of recombinant interferons and natalizumab, taking into account aspects of medical efficacy and cost-effectiveness.

Scientific background

MS is characterised by inflammatory lesions in different locations in the central nervous system (the brain, the optical nerves and/or the spinal cord) which in turn lead to a progressive destruction of the myelin sheaths of nerves and finally to axonal damage. This impairs the function of nerves to conduct electrical signals to varying degrees, manifesting as neurological symptoms and signs, such as impairment of motor function due to paralysis or ataxia, impaired sensory function, vision impairment, bladder, intestinal and sexual dysfunction, as well as to an impairment of cognitive functions and a general fatigue.
The exact causes of the disease remain elusive. It is presumed that a multifactorial genetic disposition and external trigger factors play a role in the causation of MS, which lead to an autoimmune reaction to parts of the central nervous system.
About 80% of patients have a relapsing remitting course of the disease. In most patients this phase leads to a secondary progressive MS, which is characterised by a progressive worsening of the disability with or without additional exacerbations. A small proportion of patients has a progressively worsening course of the disease without exacerbations or remissions (pri-

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mary progressive MS). It is presumed that patients with relapsing remitting MS are those who respond best to disease modifying treatment.
Disease modifying treatment aims to reduce the frequency and severity of the exacerbations and to slow the course of the disease. Interferons and natalizumab are examples of disease modifying treatments. The interferons used in the treatment of MS patients are beta-interferons, i. e. interferon beta-1a and interferon beta-1b. Natalizumab is a recombinant monoclonal antibody that blocks alpha$_4$-integrins.
The current report focuses on patient relevant outcomes. Outcomes that are important in this context to assess the effectiveness of disease modifying treatment include outcomes relating to progression, i. e. lasting worsening of the symptoms, and to exacerbations, i. e. intermittent worsening of symptoms, as well as adverse effects. A range of scales is used to measure disability and progression. The most common is Kurtzke's Expanded Disability Status Scale (EDSS). Magnetic resonance imaging (MRI) is used to study the effects of treatment on the characteristic MS lesions in the brain and spinal cord.

Research questions

Clinical effectiveness

What is the medical effectiveness of beta-interferons (monotherapy) in treating multiple sclerosis compared to placebo or other forms/dosage schemes of beta-interferon therapy? What is the effectiveness – including the long term effectiveness – of the different beta-interferons (including different dosages) with respect to patient related outcomes? Are there differences in effectiveness of the different beta-interferons and with different types of MS (relapsing remitting, secondary progressive, primary progressive)? What are the adverse effects?
What is the medical effectiveness of natalizumab in the treatment of multiple sclerosis compared to placebo or beta-interferons? What is the effectiveness – including the long term effectiveness –with respect to patient related outcomes and different types of MS (relapsing remitting, secondary progressive, primary progressive)? What are the adverse effects?

Health economic aspects

What is the cost effectiveness of interferons or natalizumab compared to other disease modifying treatments or to placebo?
What is the reason for diverging results of published cost effectiveness models?
Can the results of the cost effectiveness models be transferred to the context of the German health care system?
What influence does the consideration of indirect costs have on cost effectiveness models?

Methods

An extensive literature search was carried out (MEDLINE, MEDLINE ALERT, EMBASE, EMBASE ALERT, DAHTA, Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHS-EED), Cochrane Central Trials Register (CCTR), Cochrane Database of Systematic Reviews (CDSR), INAHTA, Ethmed, DIMDI-Superbase; dates searched were 1990 to 11/08/2006). Search terms for multiple sclerosis were combined with terms for interferons and natalizumab, as well as terms for different study types (randomised controlled trials, systematic reviews, economic evaluations) (MeSH terms and free text for each part of the search).

The full text publication of any identified citation was ordered if the titles and abstracts suggested that a) the study was a systematic review, a health technology assessment, a randomised controlled trial or an economic evaluation which assessed b) patients with MS treated with c) interferons or natalizumab. To be included, systematic reviews/health technology assessments had to fulfil a range of quality criteria; primary studies were only included when the study duration was a year or longer. Patients with any form of MS were included. Interventions were beta-interferons (interferon beta-1a or interferon beta-1b) or natalizumab as basic therapy in comparison with placebo or (in the case of interferon treatment) another beta-interferon or another dosage of beta-interferon. The emphasis of the assessment was on patient related outcomes such as progression, exacerbations, health-related quality of life or adverse effects.
Data from the included studies were extracted into standard tables. Study quality was assessed according to predefined criteria. Data were summarised in text and tables, subdivided by type of MS (early stage, relapsing remitting, secondary progressive, primary progressive) and intervention (interferon beta-1a, interferon beta-1b, interferon beta-1a vs. Interferon beta-1b, natalizumab). Results were also grouped by outcome parameter.

Results

The report summarises two systematic reviews and 24 primary studies on beta-interferon therapy. Three of the primary studies were on patients with a first demyelinating event, 14 on patients with relapsing remitting MS, five on patients with secondary progressive MS, and two on patients with primary progressive MS. Three studies on natalizumab therapy were included.
Of the high quality systematic reviews, one HTA report on immune modulatory treatment of MS included five randomised controlled trials of beta-interferon therapy, one in patients with secondary progressive MS, the remainder in patients with relapsing remitting MS. A Cochrane review assessed interferon therapy for patients with relapsing remitting MS. Both reviews found significantly better results in the interferon groups with respect to progression and exacerbations. However, the effect was moderate and the Cochrane review no longer found a significant effect when presuming that all drop-outs progressed (worst case scenario). However, the review also included treatment with interferon alpha and with beta-interferons at lower dosages than those currently licensed. Typical adverse effects of interferon therapy mentioned included flu-like symptoms and reactions at the injection site.
Most of the primary studies were of moderate quality. Most studies were described as being double blind, although the effectiveness of blinding must be questioned due to the characteristic side effects, for example the reactions at the injection site.

Multiple sclerosis (MS) early stage (first demyelinating event)

Two randomised studies reported the effects of interferon beta-1a (Rebif® (subcutaneous, ETOMS-trial) or Avonex® (intramuscular, CHAMPS-trial)) in the early stages of MS (first demyelinating event) and both reported a reduction in the conversion to definite MS during the three years of the study. Only one of the studies reported exacerbation rates and disability scores and found a lower exacerbation rate in the interferon beta-1a group, but not changes or differences in disability scores.

One randomised controlled trial reported the effects of interferon beta-1b in the early stages of MS (BENEFIT-trial) and reported a reduction in the conversion to definite MS during the two years of the study. This advantage of early treatment persisted during the three years of open follow-up, during which all patients received interferon beta-1b.

Relapsing remitting multiple sclerosis (MS)

Of the studies on relapsing remitting MS, five were two-armed comparisons of interferon beta-1a (n = 3, MSCRG-, OWIMS-, PRISMS-tiral) or beta-1b (n = 2, IFNB-MS-, Knobler-1993-trial) with placebo. The remaining interferon studies compared different doses, dosage schedules or applications of interferons (some of them including a placebo arm) or interferon beta-1a with interferon beta-1b. Only few studies compared similar doses, a fact which makes it difficult to reach conclusions regarding the effectiveness of different dosages.
With respect to progression, studies on interferon beta-1a showed a significant advantage in comparison with placebo, but not when comparing different interferon doses with each other. The rate of progression was reduced by about 10% with interferon beta-1a in comparison with placebo. For interferon beta-1b, only one study reported on progression and significant differences to placebo were not observed. Results for comparisons of interferon beta-1a and beta-1b are inconclusive. One study found no difference between interferon beta-1a and beta-1b with respect to progression, whereas another study found an advantage for interferon beta-1b (17% less progression after two years).
The data concerning exacerbations are inconclusive. When comparing different doses of interferon beta-1a or different forms of interferon beta-1a, there was no consistent difference between groups in exacerbation rates. Similarly, only two out of three studies found significant differences in favour of interferon beta-1a in relation to exacerbation rates. The situation was similar for interferon beta-1b. Two of three studies found a significant difference in the group with the higher dose of interferon beta-1b compared to placebo or a lower dose. As concerns the comparison between interferon beta-1a and beta-1b, a dose reduction study found significantly higher exacerbation rates in the dose reduction group (interferon beta-1a). Of the regular interferon beta-1a vs. beta-1b studies, one study found no difference between the two interferons, and in two studies patients treated with Avonex® (interferon beta-1a, intramuscular) had significantly higher exacerbation rates than patients treated with Betaferon® (interferon beta-1b) or Rebif® (interferon beta-1a, subcutaneous).

Secondary progressive multiple sclerosis (MS)

Patients with secondary progressive MS were examined in five studies. Three of these compared interferon beta-1a (Andersen-2004-, IMPACT-, SPECTRIMS-trial) and two interferon beta-1b (EUSPMS-, NASPMS-trial) with placebo. One of each of these studies of interferon beta-1a vs. beta-1b also compared different dosages.
Only in one of the five studies a clear effect was found with respect to progression favouring interferon beta-1a (progression reduced by about 10% at the end of the trial).
With respect to exacerbations, only two of the three interferon beta-1a and one of the two interferon beta-1b studies found a significant effect in favour of interferon compared to placebo. There was no difference between different interferon doses.

There were no data for interferon beta-1a with respect to health-related quality of life, and one study on interferon beta-1b found no significant difference at the end of the study on the multiple sclerosis quality of life inventory scale.

Primary progressive multiple sclerosis (MS)

One study each assessed the effect of interferon beta-1a (Leary-2003-trial) and beta-1b (Montalban-2004-trial) compared to placebo in patients with primary progressive MS. There was no significant difference between the groups with respect to progression, disability scores and other parameters at the end of the study. Only with regard to some MRI parameters a better result was found for interferon beta-1b compared to placebo.
Adverse effects in relation to interferon therapy comprised in all studies flu-like symptoms, fever, depression, inflammation or reactions at the injection site and myalgia. Some studies also reported adverse effects like leucopenia and increased liver enzymes. The proportion of patients who developed neutralising antibodies ranged between 2% and 50%, and several studies found no link between the presence of neutralising antibodies and the effectiveness of the medication.

Natalizumab

Evidence with respect to natalizumab mainly relates to patients with relapsing remitting MS, although one study also included patients with secondary progressive MS. In the natalizumab studies (AFFIRM-, SENTINEL-, Miller-2003-trial) a significantly lower progression was observed with natalizumab (17% to 23%) than in the comparison groups (29%). Exacerbation rates were also lower. There was no significant difference between different doses of natalizumab. Natalizumab also showed an advantage with respect to various MRI parameters compared to placebo or interferon treatment alone.
Adverse effects of natalizumab comprised fatigue, allergic reactions, reactions to the infusion, headache, infections, anxiety and peripheral oedema. However, one study reported two cases of progressive multifocal leucoencephalopathy, one of which one was fatal and the other left the patient with severe motor and cognitive damage.

Economic aspects

MS poses a high economic burden on society and for individuals suffering from it as well as on their familiesand other helpers, who bear an important part of the costs. The cost of illness in Germany has been estimated at around 40,000 Euro/patient/year. Indirect costs represent around 40% of the costs. With the more widespread use of the costly disease modifying therapies, the total costs of health care for MS are expected to rise further.
A total of 22 cost-effectiveness analyses of interferons have been summarised. No analyses on the cost-effectiveness of natalizmab were identified. The results for interferons were heterogenous, ranging from cost-savings under disease modifying treatment to incremental cost-effectiveness ratios over 1.5 million Euro per quality-adjusted life year.
All models used clinical effectiveness data from randomized controlled trials, however the assumptions made and the structure of the models differed considerably, which limits their comparability.

Discussion

Evidence regarding interferon treatment is mixed and the data suggest that beta-interferons should mainly be used in the early stages of MS and in

relapsing remitting MS. An early start of treatment is recommended by a number of authors. But interferon therapy is also linked to a considerable discontinuation rate, due to a perceived lack of effectiveness or due to adverse effects. Even though adverse effects are given as a reason for discontinuation, the literature also reports that adverse effects are generally of short duration and measures for minimising adverse effects are recommended, such as rotation of the injection site, taking non-steroidal anti-inflammatory drugs to avoid flu-like symptoms or to take the medication before going to bed. At the moment, the significance of the presence of neutralising antibodies is unclear.

There are only few studies with a real long term follow-up (i. e. more than ten years). These few studies suggest however that beta-interferons do maintain their effectiveness in the longer term and improve overall prognosis.

Despite the promising results regarding the effectiveness of natalizumab, any statements about this drug have limited validity. The duration of one of the studies was too short to allow conclusions about long term effectiveness. In addition, a follow-up assessment in this study after one year showed no remaining advantages of the natalizumab treatment. The existing longer term studies are not comparable as one study assessed natalizumab as monotherapy and the other as combination therapy with interferon beta-1a (Avonex®, intramuscular). Safety aspects also warrant caution. Apart from the two cases of progressive multifocal leucoencephalopathy that have been reported, a further case of a fatal progressive multifocal leucoencephalopathy occurred after natalizumab treatment in a patient with Crohn's disease. In some cases natalizumab may obviously impair immune function to such an extent that it increases the danger of fatal opportunistic infections. The risk during long term treatment has so far not been assessed and can therefore not be predicted.

In summary, the economic evaluations reviewed leave a great degree of uncertainty concerning the estimates for the cost-effectiveness of interferon treatment. There was no consensus concerning the inclusion of indirect costs in the analysis. However, the effect of including indirect costs in the existing models would probably be moderate. None of the estimates has been produced with German data which limits conclusions for the German health care system.

Conclusion

Current evidence suggests that treatment with either type of beta-interferon has a moderate effect on exacerbation rates. However, the benefit is so small that the individual patient cannot experience it as new exacerbations will occur despite therapy. This, in combination with frequent and unpleasant adverse effects leads to high discontinuation rates. In direct comparison trials, interferon beta-1b (Betaferon® or Betaseron®) and interferon beta-1a (Rebif®, higher dosage of 44 µg three times per week subcutaneous) proved superior to interferon beta-1a (Avonex®, 30 µg in one intramuscular injection per week) with respect to exacerbation outcomes. Because of the lack of long-term studies, the effect on disease progression is uncertain. The long-term economic benefits or costs of interferon treatment are also uncertain, in particular with regard to the German context as no economic evaluations have been carried out using German cost data.

The long-term effectiveness of natalizumab treatment has not been demonstrated and there are severe concerns about its safety due to reports of progressive mulifocal leucoencephalopathy that occurred under treatment. Economic evaluations for treatment with natalizumab are not available.