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Multiple Sclerosis (MS) Class Update

Month/Year of Review: March 2012
PDL Class: Neurologic: MS Drugs
Current Status of PDL Class:

- Preferred Agents: Interferon beta-1a IM (Avonex®), Glatiramer Acetate SC (Copaxone®)
- Non Preferred: Interferon Beta-1b SC (Betaseron® and Extavia®), Interferon beta-1a SC (Rebif®), Natalixumab IV (Tysabri®), Mitoxantrone IV

Previous HRC Conclusions (May 2008):

1. All included drugs are modestly effective compared to placebo in relapse prevention and disease progression.
2. There is no evidence of clinical superiority of any of the studied drugs.
3. Limited data suggests that neutralizing antibodies (in β-interferon therapy) may negatively affect relapse rate 3-4 years after treatment.
4. There was no difference in withdrawal rates among studied drugs noted; however, in general adverse event reporting was poor.
5. For β-interferons:
    a) There is insufficient evidence to determine a comparative difference between the β-interferons for flu-like symptoms.
    b) There is insufficient evidence to determine a relative difference in ALT elevations for the β-interferons.
6. Interferon β1a IM (Avonex®) appears to have a lower injection site reaction compared to the other β-interferons and glatiramer acetate.
7. Therapy related acute leukemia was reported in 2/1620 patients (both were women) taking mitoxantrone.
8. Estimates of progressive multifocal leukoencephalopathy (PML) incidence with natalizumab (Tysabri®) use is 1.0/1000 patients based on three known cases. Because of concerns regarding this, the company instituted a risk management plan in cooperation with the FDA known as the TOUCH prescribing program. Patients may only get this medication through this program.
9. There is insufficient evidence to determine a comparative difference between the β-interferons in reducing the probability of converting from clinically isolated syndrome (CIS) to clinically definite MS. There is no data on prevention of conversion for any of the other included drugs.

Reason for Review:

In 2008, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the disease-modifying drugs (DMDs) for MS. Since this review, in 2010 the Oregon Evidence-based Practice Center (EPC) Drug Effectiveness Review Project (DERP) completed an updated report for the drug class review.[1] This full report can be found on the Oregon EPC website at http://derp.ohsu.edu/about/final-document-

display.cfm. There were also two new medications FDA approved indicated in the treatment of MS. Fingolimod (Gilenya®) is the first oral DMD indicated for patients with MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[2] Dalfampridine (Ampyra®) was approved to improve walking in patients with MS.[3] Dalfampridine is not indicated to decrease relapse rate or prevent the accumulation of disability. These individual drug monographs can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings. In 2009, the FDA also approved Extavia, a new branded version of interferon beta-1b, which is the same product as Betaseron and contains the same active ingredient.[4]

Conclusions:

The DERP MS class update concluded that there was fair evidence that interferon beta-1a IM (Avonex®) is less effective than interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) for preventing relapse in patients with relapsing remitting multiple sclerosis (RRMS) based on four fair-quality head-to-head trials. Interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) were similarly efficacious for preventing relapse.[1] There was conflicting evidence in disease progression outcomes between the interferons, and it is likely that any differences are small and clinically insignificant. Overall evidence was moderate for patients with relapsing remitting MS while the strength of the evidence in other populations was low. On other outcomes and in other populations, direct evidence is either lacking or shows few differences in effectiveness or safety among the DMDs used to treat MS, including in progressive forms of MS and in patients with clinically isolated syndrome.

There was also fair quality evidence that interferon beta-1a IM (Avonex®) appears to have the lowest immunogenicity compared to the other beta-interferons. While there is insufficient evidence to conclude there is an impact on disease progression, there was fair quality evidence that consistent positive neutralizing antibody status with high titer adversely affects the impact of these drugs on relapse rates during long periods of follow-up. No studies met criteria to be a true effectiveness study and applicability of the results remains limited. There was insufficient evidence to determine a comparative difference in subpopulations. There was also moderate evidence that the beta interferons are similar in harms and discontinuations due to adverse events, while adverse event reporting remained poor.[1]

The American Academy of Neurology, the National MS Society, and the National Institute for Clinical Excellence recommend first line treatment with glatiramer acetate or an interferon beta in MS patients.[5–7] The clinical guidelines have not been updated to reflect the place for oral fingolimod. The best evidence for effectiveness is in patients with RRMS, but therapy may also be considered in certain patients with clinically isolated syndrome and progressive disease.

Recommendations:

- Due to similar efficacy and potential difference in relapse outcomes between the interferon products, evaluate costs of interferon beta-1a SC (Rebif®), interferon beta-1b SC (Betaseron® and Extavia®), and interferon beta-1a IM (Avonex®) for further decision making.
- Include dalfampridine (Ampyra®) as a non-preferred agent on the PDL and include clinical criteria for use including:
    - Has a walking disability that requires the use of a walking aid.
    - Be able to complete the T25FW in 8-45 seconds.
    - Does not have renal impairment or a history of seizure disorder or epileptiform activity on an EEG.

- Include fingolimod (Gilenya®) as a non-preferred disease modifying medication for MS and develop clinical criteria to restrict based on the following:
    - Prescribed by or in consultation with a neurologist
    - Patient has relapsing remitting MS
    - Is not currently on therapy with an injectable DMT
    - Has failed or cannot tolerate a full course of a first line interferon or glatiramer

Background:

MS is an inflammatory disease of the central nervous system and the vast majority of patients with MS have relapsing-remitting MS. The majority of available direct evidence continues to reside in patients with relapsing-remitting MS rather than progressing forms MS. Progression of MS is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) the most widely used validated measure of disability and is often a primary clinical outcome in MS clinical studies. The scale ranges from 0 to 10, with <6 indicating the patient can walk without aid for limited distance, 6-8 indicating patient is severely restricted in movement with aids or assistance, and > 8 indicating a person is restricted to a bed. Treatment of MS falls into three main categories: symptomatic therapy to improve the patient's quality of life, treatment of acute attacks, and DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with corticosteroids and symptoms are treated accordantly with appropriate agents. The development of neutralizing antibodies to interferon beta medications may lead to a decreased efficacy of these agents. However, the long term impact of neutralizing antibodies on clinical outcomes has not been fully determined.

DMDs are indicated to prevent relapses and progression of disability and modify the immune response through immunomodulatory or immunosuppressive effects. There are currently 5 injectable DMDs available and one oral. Four of the disease modifying medications are type 1 beta interferons and include interferon beta-1b SC (Betaseron® and Extavia®) and interferon beta-1a IM and SC (Avonex® and Rebif®). In 2009, the FDA approved Extavia® with the same active ingredient and registration trials as Betaseron 250 mcg. The 5th agent is glatiramer SC and fingolimod is the first oral DMD. Natalizumab IV and mitoxantrone IV are also FDA-approved for the treatment of RRMS. Natalizumab and mitoxantrone are

not recommended for first-line use due to safety concerns with progressive multifocal leukoencephalopathy and cardiotoxicity, respectively. Natalizumab is reserved for patients with rapidly advancing disease who have failed other therapies.

Currently there are four other oral therapies in addition to fingolimod in development for the treatment of relapsing-remitting MS and while better patient compliance is expected with the oral agents compared with the injectables, the safety profiles of these new oral drugs will have to be monitored carefully.[8] In December of 2011, the FDA released a drug safety review of a reported death within 24 hours of taking the first dose of fingolimod.[9] Reports of eleven deaths through November 2011 in patients taking fingolimod have prompted a safety investigation.[10] There is no evidence yet that the drug was responsible for the deaths. Heart rhythm and electrical conductivity abnormalities are both recognized risks after initial dosing.[10]

Methods:
A literature search was conducted since the end of the literature included in the DERP report for new randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of MS. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. After review of the 99 total citations resulted from Medline OVID search, 2 new relevant head-to-head trials, 2 new systematic reviews from the Cochrane Library, 1 systematic review from the Oregon Evidence based Practice Center, and three new FDA safety alerts were identified and evaluated.

Systematic Reviews:

DERP:

In patients with RRMS, there were five fair quality head-to-head trials providing direct evidence for the comparative efficacy of the beta interferons. This included the addition of one since the 2008 MS class review.[1] Overall, these studies supported the use of the beta interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes. These trials found higher rates of patients who were relapse free in the interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®) groups compared with interferon beta-1a IM (Avonex®) and disability-related outcomes were not found to be statistically significant (Betaseron vs. Avonex; % relapse-free RR 1.51, 95% CI 1.11 to 2.07; NNT 6).[1]

There were two fair quality and one good quality trial comparing glatiramer to another DMD (no direct evidence in previous report), 2 comparing to interferon beta-1b (Betaseron®) and 1 comparing to interferon beta-1a (Rebif®). In the direct comparison studies, no significant differences were found in relapse-related or disease progression outcomes, while previous observational studies that compared glatiramer to the interferons

found a significantly greater reduction in relapse rate at 2 years with glatiramer.[1] Further good-quality direct comparison studies are needed to further confirm the direct findings.

There were no studies comparing natalizumab or mitoxantrone to another DMD for relapsing-remitting MS, and both were more effective than placebo for both disease progression and relapse rate based on a small number of trials. On other outcomes and in other populations with progressive forms of MS, direct evidence is either lacking or shows few differences in effectiveness among the DMDs. Only indirect evidence is available in patients with secondary progressive MS and primary progressive MS.[1]

Two new key questions were identified for the update evaluating the importance and effects of interferons on neutralizing antibodies.[1] Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness. There was fair quality evidence that interferon beta-1a IM appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2-8.5% reported, starting around 9 months of treatment, while evidence displayed that interferon beta-1a SC antibodies occur at rates from 12% to 46% of patients. With interferon beta-1b SC (Betaseron®), neutralizing antibodies appeared as early as 3 months in 30% to 40% of patients. There is fair quality evidence that consistent positive neutralizing antibody status with high titer adversely affects the impact of these drugs on relapse rates during long periods of follow-up (> 2 years) and there is insufficient evidence to conclude there is an impact on disease progression.[1]

There is fair quality evidence that there is no difference in withdrawal rates among beta interferons in head-to-head trials, although adverse events were generally poorly reported. Withdrawal rates ranged from 3% (glatiramer) to 9% (Betaseron®) in placebo controlled trials.[1] Although generally well tolerated, adverse events were reported frequently with all three beta interferon products and differences between the products were evident. Interferon beta-1b IM (Avonex®) had higher rates of flu-like syndrome (62.2% vs. 41.7% Betaseron vs. 28.7% Rebif), fatigue, and depression while interferon beta-1a SC (Rebif®) had much higher rates of injection site reactions compared to the other interferons (60.6% vs. 58.9% Betaseron vs. 8.5% Avonex).[1]

Compared to beta interferon, glatiramer showed similar tolerability with higher rates of injection site reactions and post-injection systemic response. Long term safety data demonstrate that lipoatrophy is associated with prolonged use of glatiramer.[1] In placebo controlled trials, mitoxantrone use was associated with amenorrhea, nausea and vomiting, and urinary tract infections, and a non-significant decrease in left ventricular ejection fraction below 50% which associated with higher cumulative doses in a subgroup analysis, although this did not reach statistical significance (P=0.06). Risk of permanent amenorrhea may be associated with older age (odds ratio 1.18 95% CI 1.10 to 1.27; p=0.01) and higher cumulative dose (odds ratio 1.02, 95% CI 1.01 to 1.04; p=0.01) based on 1 observational study (N=189).[1]

Natalizumab has been linked to progressive multifocal leukoencephalopahy (PML) and now contains a black box warning with risk directly proportional to cumulative dose. In March 2011, a FDA safety alert revised the drug label to warn of the risk of PML in patients taking natalizumab for treatment of MS and Crohn's Disease. This alert also included information on a newly identified risk factor for the development of PML. Patient's who took an immune system suppressing medication prior to natalizumab have been shown to be at an increased risk for developing

PML.[11] The label previously included that there was an increased risk for using an immune suppression medication at the same time as natalizumab. In January of this year an additional FDA safety communication was released informing the public that testing positive for anti-JC virus antibodies is an additional risk factor for PML.[12] Patients with all three risk factors (presence of anti-JC virus antibodies, longer duration of treatment (beyond 2 years), and prior or current treatment with an immunosuppressant medication have an estimated risk of PML of 11/1,000 users.[12]

There is some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors one product over another. There is insufficient data to make conclusions about the use of these drugs in other subpopulations based on demographics, socioeconomic status, other medications, severity of disease, or co-morbidities.

Cochrane Library:

La Mantia, et al. aimed toward determining clinical efficacy and safety of glatiramer in patients with MS by evaluating all RCTs comparing glatiramer and placebo in patients with both relapsing remitting and progressive MS.[13] Based on 6 efficacy trials, in patients with relapsing remitting MS a decrease in the mean EDSS score was found without any significant effect on sustained disease progression. Three trials were given a full score on the Jadad quality rating scale and two were given a score of three due to unclear allocation concealment and insufficient details on blinding. In patients with RRMS, a slight decrease in the EDSS score favored glatiramer at two years (mean difference -0.33 95% CI -0.58 to -0.08, p=0.009) and at 25 months (-0.45, 95% CI -0.77 to -0.13, p=0.006). The reduction of mean number of relapse was also evident. Relative risks of experiencing no exacerbation were 1.28 at 1 year, 1.39 at 2 years, and 1.33 at 35 months (p=0.03, p=0.06, p=NS, respectively).[13] No benefit was seen in patients with progressive MS on relapse outcomes or disease progression, based on five hundred and forty patients in the analysis.

A second Cochrane review evaluated interferon beta in patients with secondary progressive multiple sclerosis (SPMS) compared to placebo in disease progression and concluded that there is high quality evidence that interferon does not prevent the development of permanent physical disability in SPMS and its anti-inflammatory effect is unable to hinder progression.[14] Based on five RCT's and 3122 treated patients, interferon therapy did not decrease the risk of progression at sustained 6 months (RR 0.98, 95% CI 0.82 to 1.16) after three years of treatment. A significant decrease in the risk of progression sustained at 3 months (RR 0.88, 95% CI 0.9 to 0.97) and in the risk of developing new relapses at three years (RR 0.91, 95% CI 0.84 to 0.97) were found.[14]

Randomized Controlled Trials:

One new open-label, fair quality, randomized controlled trial compared the efficacy of interferon beta-1a (Avonex, REbif) and interferon beta 1-b (Betaseron) in 90 individuals with MS on the expanded disability status scale (EDSS) and relapse rate.[15] There was no statistical difference in reducing EDSS shown by the average EDSS change from baseline (Avonex 1.28, Betaseron 1.30, Rebif 1.28, p=0.998). There was no significant difference in the decrease in relapse rate between the three treatment groups (Avonex 0.40, Betaseron 0.60, Rebif 1.2, p-0.447). This study included a higher proportion of females compared to previous studies and included patients with an average lower age of onset (31.11 years).

Another RCT compared the efficacy of mitoxantrone induction therapy prior to interferon beta-1b SC with interferon beta-1b SC alone in patients with aggressive relapsing-remitting MS on the time to worsen by at least one EDSS point confirmed at 3 months.[16] Due to the associated adverse effects, it was not possible to double blind the intervention, and results should be interpreted with caution. Only the clinical outcomes were evaluated in a blinded fashion. In the group receiving mitoxantrone induction therapy, the time to a >1 EDSS point was delayed ($p<0.012$) and the proportion of patients who remained relapse-free was increased compared to the interferon group (52.7%, 27.8%, $p<0.008$, NNT 4).[16] Overall, patients receiving mitoxantrone had a higher incidence of adverse events, including upper respiratory tract infections, leukcopenia, nausea, and reduced ventricular ejection fraction. The overall dropout rate was quite high at 44%.

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