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Assessing risks of multiple sclerosis therapies

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ABSTRACT

Over the last two decades, thanks to the discovery of several pharmaceutical agents, multiple sclerosis (MS) has been transformed into a treatable disorder although the degree of therapeutic response may vary considerably. As more medications find their entry into the MS market, a clinician faces a mounting challenge of comparing risk and benefit profiles of various agents in an attempt to find the best treatment approach for each individual patient. In this review, we aim to summarize the available data on safety profiles of available MS therapies while focusing mostly on serious medication specific potential adverse events without discussing the teratogenic potential of each agent (unless there is a black box warning) or hypersensitivity reactions. Our goal is to provide a clinician with guidance on assuring the appropriate safety monitoring for patients treated with one of the agents discussed. We also comment on the future of risk management in MS and discuss possible enhancements to the current model of drug approval process and general strategies to improve the patient safety.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder affecting the central nervous system that commonly results in progressive accumulation of disability. Over the last two decades, thanks to the discovery of several pharmaceutical agents, this disease has been transformed into a treatable disorder although the degree of therapeutic response may vary considerably. As more medications find their entry into the MS market, a clinician faces a mounting challenge of comparing risk and benefit profiles of various agents in an attempt to find the best treatment approach for each patient.

Since MS is a chronic disorder that most of the time requires prolonged exposure to a therapeutic agent, knowledge of safety profiles of available therapies becomes of utmost importance since the risk of developing an adverse event can be augmented with the duration of treatment. Unfortunately, phase III trials are generally designed to evaluate efficacy and not necessarily occurrence of rare side effects. This can make the assessment of treatment safety profiles challenging at times. In addition, on the contrary to other diseases with grimmer prognosis, such as cancer, MS is not a fatal disorder and, hence, risk tolerance tends to be lower for MS patients and their treating physicians alike, although some available therapies are used in both conditions (mitoxantrone).

As a result of a flurry of recent highly publicized reports of medication withdrawals from the market secondary to safety concerns, there is an increased awareness and fear of medication adverse events among patients and health care professionals. These events also gave rise to a widely held impression that the pharmaceutical industry could downplay safety risks. Thus, drug-regulatory agencies frequently call for increased regulation to assure the patient safety [1]. These elements contribute to the increased government regulation of the industry that may result in decreased availability of new therapies leading to increased frustration of patients and physicians. In the end, the burden lies on shoulders of doctors to critically evaluate the available information with the goal of coming up with an optimal treatment strategy that satisfies the risk–benefit ratio requirements of the individual patient and the physician.

In this review, we aim to summarize the available data on safety profiles of available MS therapies while focusing mostly on serious medication specific potential adverse events without discussing the teratogenic potential of each agent or hypersensitivity reactions. Our goal is to provide a clinician with guidance on assuring the appropriate safety monitoring for patients treated with one of the agents discussed. Finally, we comment on the future of risk management in MS and discuss possible enhancements to the current model of drug approval process and general strategies to improve the patient safety.

2. Interferon beta

Interferon beta (IFNb) is one of the most commonly prescribed therapies for relapsing remitting MS (RRMS). Although considered to be generally safe, certain adverse events are possible and, thus, regular monitoring is recommended.

Up to 75% of patients experience flu-like symptoms such as fever, headache, muscle pain, fatigue, and chills [2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally effective.

The most common observed laboratory abnormalities are elevation of liver enzymes and leukopenia [3–9]. These changes are seldom serious, generally reversible, and most of the time do not require the discontinuation of therapy [8,9]. However, reports of fulminant liver

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failure as well as reports of unmasking of preexisting autoimmune hepatitis or psoriasis do exist [10–13]. Hence, the recommendation for regular monitoring of liver enzymes is maintained. Complete blood count with differential and complete metabolic panel that includes liver function tests should be obtained monthly in the first 3 months with quarterly checks for the rest of the first year of treatment [2]. Thereafter, provided no laboratory abnormalities have been observed, the blood work can be performed on a semi-annual to annual basis. If significant laboratory abnormalities are found while under treatment, lowering the medication dose or even temporary discontinuation of therapy would have to be considered.

A syndrome resembling thrombotic thrombocytopenic purpura (TTP) with fever, thrombocytopenia, and renal failure has been reported in two women treated with IFNb-1a for MS [2]. One of the authors (VP) has also taken care of a male patient that has developed a TTP-like syndrome that was thought to be possibly related to IFNb-1a 3×44 μg/week therapy since it was the only medication that patient was taking at the time. The hospital course was very complicated, but the patient did eventually have a good recovery with plasma exchange treatment. Therefore, patients should be counseled on the importance of talking to their doctors if they experience excessive fatigue and fever that are out of proportion to the usual interferon treatment associated flu-like symptoms, especially if accompanied by a decrease in urine output.

Reports of depression associated with interferon therapy are well known, however controversy still exists, since depression is quite common in MS patients in general, whether they are treated with IFNb or not. A recent review has described eleven cases of severe depression with suicide attempts among MS patients treated with interferon beta who had no prior psychiatric history [14]. On the other hand, other studies found no evidence to support the claim that IFNb can cause or exacerbate depression [15]. Regardless, all MS patients need to be screened for signs of depression and if those are present, appropriate treatment should be instituted (antidepressant, psychiatry evaluation, etc). Inquiring about patient's mood should be an integral part of any follow-up visit, especially if patient is treated with IFNb.

3. Glatiramer acetate (GA)

Glatiramer acetate is a random polymer of glutamic acid, lysine, alanine, and tyrosine. The most common side effect, aside from local injection site reactions, is a post-injection reaction that may happen to 10–15% of patients that is manifested by chest tightness, shortness of breath, palpitations, anxiety and flushing lasting 15–30 min [16]. These events have not been associated with any cardiovascular or other systemic consequences. Educating the patient on this possible side effect is important in order to relieve the potential anxiety should this event take place. GA has not been associated with liver function abnormalities, leukopenia, or depression [16,17].

4. Mitoxantrone

Mitoxantrone is an anthracenedione that is used to treat several types of cancer [18]. It has also shown efficacy in the treatment of worsening relapsing–remitting or secondary progressive MS [19]. Mitoxantrone is usually given intravenously at a dose of 12 mg/m^2 every 3 months until a maximum cumulative lifetime dose of 140 mg/m^2 is reached, although lower cumulative doses are commonly used [20]. Mitoxantrone is a good example that emphasizes the importance of continued post-marketing safety evaluation since figures from initial studies may often misrepresent the actual occurrence of adverse events. Significant potential safety concerns have been found with this agent and were discussed in detail in a recent review [20].

Cardiotoxicity is a well known potential complication of mitoxantrone therapy with patients developing varying degrees of cardiac dysfunction ranging from an asymptomatic decrease in left ventricular ejection fraction (LVEF) to congestive heart failure (CHF). This applies to both cancer and MS patients treated with this agent. Initial safety data from the original study were fairly reassuring, however a number of Class III studies documented generally higher cardiotoxicity in mitoxantrone-treated MS patients although the reported frequency, severity, and time course of cardiac complications varied significantly [20–32]. Consolidating the data from these studies gives an estimated 12% rate of decreased LVEF and 0.4% risk of CHF, although the differences in mitoxantrone regimens and cardiac monitoring between different centers make this figure more of an approximation [20]. RENEW, an ongoing phase IV study of mitoxantrone is aimed at assessing the long-term safety and tolerability of treatment. As of January 2008, CHF was noted in 2% of the observed patients while 13% of patients, for whom serial cardiac function results were available, had LVEF < 50%. A general recommendation is to obtain a baseline assessment of LVEF prior to the initial treatment and if it is found to be less than 50% or if a patient has any history of cardiovascular disease, treatment should be withheld. In terms of subsequent monitoring, an assessment of LVEF should be performed before each dose and treatment needs to be stopped if decrease in systolic function is found. Since the total cumulated dose of mitoxantrone is thought to influence the cardiotoxic effect, the upper dose limit should be strictly defined for each patient. In 2008, the U.S. Food and Drug Administration (FDA) made the further recommendation that patients undergo annual cardiac function assessment after completing mitoxantrone treatment due to the potential for delayed cardiotoxicity [20].

Another potential dreaded complication of mitoxantrone therapy is treatment related acute leukemia (TRAL). The majority of TRAL cases in the MS population occur within a few years of mitoxantrone use. Initially, the risk of TRAL in MS patients was estimated to be 0.07% after a mean follow-up of 36 months in 1378 patients [33]. However, a more recent number of Class III and IV case series and case reports have suggested a higher risk of TRAL than previously thought [34–48]. Combining the data from the series above will give an estimated TRAL risk of 0.81%, although the fact that this number is merely an approximation has to be once again emphasized since the length of follow-up was quite variable among the studies [20]. A recent Italian multicenter retrospective study reported the risk of TRAL of 0.93% with an additional observation that patients who developed TRAL had received a higher mean cumulative dose of mitoxantrone than patients who did not [43].

In terms of routine monitoring, complete blood counts are recommended prior to each infusion and if patient develops an infection since leukopenia is quite common and patients are considered to be immunosuppressed when treated with mitoxantrone. Because this agent is eliminated primarily via biliary excretion, complete metabolic panel with liver function tests should be performed as well prior to each treatment. Pregnancy test is also recommended prior to each treatment due to teratogenicity of this medication.

5. Natalizumab

Natalizumab is a monoclonal antibody directed against alpha-4-integrin that is approved as a second-line treatment of RRMS in patients who either fail first-line treatment or who have highly active disease. In MS clinical trials, infectious complications other than progressive multifocal leukoencephalopathy (PML) were infrequent, however, frequency of herpes infections, pneumonia, and urinary tract infections was slightly higher in patients treated with natalizumab [49,50]. Therefore, patients need to be advised on reporting signs/symptoms of serious infections to their physicians. A potential complication of treatment with this agent that received most attention is PML, which is an opportunistic viral infection of the central nervous system caused by the human polyoma JC virus (JCV) [51,52]. With the advent and more wide-spread use of new immunosuppressive therapies to treat various autoimmune disorders, this disease that was previously seen mostly in AIDS and cancer patients, has become more common and better