

## **Disease Modifying Therapies for MS**

The term “disease-modifying therapy” (DMT) means a drug that can modify or change the course of a disease. In other words a DMT should be able to reduce the number of attacks and/or also slow down the disease from progressing.

### **50. What are disease modifying therapies (DMT)?**

Currently, eight drugs (or DMTs) have been approved by the FDA for the treatment of relapsing-remitting and relapsing forms of MS.

<b>Generic name</b>	<b>Market name</b>	<b>Year Approved</b>
IFN beta-1b	Betaseron ®	1993
IFN beta-1a	Avonex <sup>TM</sup>	1996
Glatiramer acetate	Copaxone ®	1997
Mitoxantrone	Novantrone ®	2001
IFN beta-1a	Rebif ®	2002
Natalizumab	Tysabri ®	2006
IFN beta-1b	Extavia®	2009
Fingolimod	Gilenya®	2010

At this time, there is no FDA approved DMT for PPMS. Based on individual case scenario, the neurologist may consider some treatment options in an attempt to slow the disease progression. However, there needs to be a clear understanding that there is no large study which has unequivocally established the effectiveness of any therapy for PPMS. Novantrone was approved by the FDA in 2001 for worsening RRMS or progressive relapsing MS.

### **51. How soon should treatment start in RRMS?**

It is likely that patients may benefit from early treatment. The majority of MS experts encourage early treatment once the diagnosis of RRMS is confirmed or as soon as the clinical event suggestive of MS has occurred with all investigations pointing towards the diagnosis of MS. There is significant data to support the benefit of early treatment in patients who have experienced just one attack of MS but have MRI evidence to support the likelihood of developing MS in the future. These patients with just a single attack are sometimes referred to as having “Clinically Isolated Syndrome” (CIS). Most experts agree that CIS simply represents the earliest stage of MS i.e. relapsing-remitting MS.

### **52. How does interferon-beta therapy work?**

Most data suggest that IFN beta works by healing the blood brain barrier (the passage through which blood is carried into the brain). This healing prevents the inflammatory cells of the immune system from entering the brain. These cells are called lymphocytes and could be potentially harmful to brain and spinal cord proteins (in this case, myelin proteins and axons). There may be other ways by which IFN beta therapy may be helpful in MS.

### **53. How does Copaxone work?**

There are several mechanisms by which Copaxone may work in MS. Recent data suggest that it works by changing the harmful inflammatory cells into the non-inflammatory healing cells of the immune system. These healing cells have been shown in the animal model to penetrate in the brain and minimize inflammation. Further work is ongoing to understand this unique property of Copaxone.

### **54. How does Tysabri work?**

Tysabri is a drug that blocks the passage of inflammatory cells of the immune system from entering the brain and the spinal cord.

### **55. How does Novantrone and other chemotherapy drugs work?**

Chemotherapy drugs are used in MS to suppress the immune system. By doing so, it is assumed that harmful cells of the immune system will be killed and not cause inflammatory damage in the brain and spinal cord.

### **56. How does Gilenya work?**

Gilenya works by “trapping” immune system cells (lymphocytes) in the lymph nodes and other lymphoid tissue. These cells stay trapped in the lymphoid tissue as long as the drug is taken but the effect is reversible within a few weeks after stopping the drug. It is believed that the immune system cells continue to perform their immune activities although more information is needed regarding the long-term safety.

### **56. Is one drug better than the other?**

Comparative data is conflicting. Several studies have suggested that interferon beta given at high doses and more frequently such as Betaseron® or Rebif® may be superior to low-dose weekly interferon beta (Avonex™) in reducing the frequency and risk of having relapses. Other studies have contradicted these observations and have suggested that dosing and frequency of interferon-beta has no impact on the relapse rate in RRMS. Similarly, there is no convincing study to suggest that Copaxone is better or less effective than interferon beta therapy in RRMS. Since MS is a lifelong disease, one needs to keep in mind the long-term effect of these therapies, their safety for long-term use, and their ability to reduce sustained tissue damage in the brain and spinal

cord. Achieving these goals can be difficult in an individual patient and should be discussed in detail when choosing a therapy.

Tysabri is another promising therapy that is the most recent drug to be approved by the FDA for use in relapsing MS. However, long-term data with Tysabri is lacking and there are no head to head studies to compare it with interferon-beta or Copaxone.

Recently, two large head to head studies with almost 3000 MS collectively enrolled, demonstrated that interferon beta (Betaseron® or Rebif®) and Copaxone® were similar in their effect on reducing the frequency and risk of having relapses. Similarly, they also showed a similar effect in slowing the disease from progressing. These two studies suggest that in early and mildly affected MS patients, all therapies seem to be very effective.

### **57. Is it possible to combine drugs to achieve a better effect?**

This is a major focus in the coming years to achieve better efficacy by combining drugs. Preliminary studies suggest that the combination of interferon beta and GA is safe. However larger studies, which are currently ongoing, are needed to confirm that the combination therapy is clinically effective. Other trials are also underway examining a variety of combinations.

### **58. What are the side effects of Interferon beta?**

Most of the side effects can be managed by careful blood test monitoring and use of over the counter drugs such as ibuprofen or acetaminophen. However, if side effects persist, then alternate therapies should be considered.

- Injection site reaction (redness, itching, pain)
- Injection site necrosis, though rare, can be seen with Betaseron® and Rebif®
- Flu-like symptoms (fever, chills, muscle pain, malaise)
- Abnormal white blood count and liver function tests
- Menstrual disorders (see *fertility issues*)
- Depression
- Fatigue
- Spasticity (may worsen preexisting stiffness)

### **59. What are the side effects of Copaxone?**

- Injection site reaction (redness, itching, pain)
- Immediate post-injection reaction that occurs in approximately 10% of patients. This reaction includes chest discomfort, flushing, palpitations, or shortness of breath which start within few minutes of the injection and resolve spontaneously within a half-hour; it has never been reported to have any serious consequences. This reaction does not constitute an allergic reaction. Patients can continue with their injection therapy.

## **60. What are the side effects of Tysabri?**

- Over all, the IV infusion of Tysabri is very well tolerated. Patients may experience occasional abdominal bloating and headache. However, these are mild and transient.
- During the infusion, patients may experience “infusion reactions” that usually involve rash, chills, and general uneasiness. Usually, these are mild but occasionally can be severe and require immediate assessment. In such cases, these reactions may be allergic in nature requiring discontinuation of therapy. In the original clinical trials of Tysabri, 3 out of 3000 patients taking Tysabri combined with another drug developed a very serious brain infection called Progressive Multifocal Leukoencephalopathy (PML). Two of those 3 patients with PML died. The exact risk of developing PML using Tysabri alone (not in combination with other drugs) is unknown at this time; however the risk is assumed to be around 1 in 1000. Patients on Tysabri may be at risk for other serious but yet unknown infections.
- As of August 2011, 150 patients with PML have been reported world wide who received treatment with Tysabri. This data is updated on a monthly basis but overall with more than 100,000 patients treated with Tysabri, the rate of PML remains at approximately 1 in 1000.
- On August 15, 2011, a blood test to evaluate the risk for developing PML was approved by the FDA. This blood test detects antibodies made by the immune system against the JC virus that causes PML. Thus far, data from thousands of patients indicates that approximately 50% of the patients (and general population) test positive for the antibody. If tested positive, the risk for developing PML is considerably higher than a patient who tests negative. This information can be very helpful in planning treatment with Tysabri as well discontinuing treatment with Tysabri.
- Patients receiving Tysabri are registered in a national program (TOUCH program) monitored by the manufacturers (Biogen Idec) and reported periodically to the FDA. This program requires that every serious adverse event experienced by a patient receiving Tysabri, be reported to the TOUCH program.

## **61. What are side effects of Novantrone and other chemotherapy drugs?**

Novantrone and cytoxan are chemotherapy agents used in MS that are administered in an outpatient infusion center. They can not be given at home by home infusion nurses. Usually, it can take up most of the day to complete the infusion. All patients should follow instructions given by the doctor very closely and report any new symptoms and side effects promptly.

Novantrone is usually administered every 3 months at a fixed dose until a total dose of 140 mg/m<sup>2</sup> has been given. Higher doses are associated with heart failure. Before every dose of Novantrone, an echocardiogram should be performed to assess the cardiac status of the patient. If the cardiac output function declines below a pre-specified level,

then Novantrone should be discontinued. Once a dose of 140 mg/m<sup>2</sup> is reached, no further dose of Novantrone should be given.

Another chemotherapy drug called cytoxan is usually given once a month and can be given for 6 months to a year. It also requires careful monitoring although there are no known cardiac side effects associated with cytoxan.

The most common side effects reported with chemotherapy drugs used in MS including Novantrone or cytoxan are:

- Decrease blood count (CBC) with a possible risk of infections
- Abnormal liver function tests (LFTs)
- Fatigue
- Nausea and vomiting
- Hair thinning and hair loss
- Cardiac toxicity (seen only with Novantrone)
- Bladder irritation (seen only with cytoxan)
- Menstrual cycle abnormalities and loss of menstruation (usually temporary)
- Treatment related leukemia (reported with Novantrone)
- There is a remote possibility of cancers (associated with cytoxan)

Despite the list of side effects, chemotherapy can be a highly effective short-term measure to stabilize rapidly worsening MS. Therefore, it is important to discuss the benefits versus risks with the doctor in a careful manner and obtain a second opinion if necessary.

### **63. What are the side effects of Gilenya?**

As with most drugs that are approved by the FDA, the vast majority of the patients usually tolerate the drug well without any significant problems. However, due to the effect of the drug on a variety of body systems, patients need to be monitored closely and regularly. Furthermore, because the drug has been approved for a short period of time (September 2010), long term data is still needed. Common and serious side effects that may be associated with Gilenya include:

- Infections
- Slow heart rate with the first dose
- Swelling behind the eyes (macular edema)
- Malignancies
- Difficulty with breathing
- Liver injury
- Immunosuppression

### **62. How can I know if a drug is working for me?**

Evaluating if a DMT is working can be difficult. A patient often needs to be on a medication for at least a year or two before a determination can be made. Generally speaking, if the patient is experiencing fewer or no attacks with no signs of disease progression, then in all likelihood, the patient is responding to therapy. This information combined with periodic MRI scans can be very helpful in assessing if a particular therapy is working.

### **63. How long should a patient take DMTs?**

This question is often raised by patients, especially those who have been on therapies for several years. The current view is that patients should be on therapy all the time in order to reduce the inflammatory and degenerative damage from the disease. Only during pregnancy, are women encouraged to go off therapy. However, until careful studies are conducted to address this issue, patients should remain on DMT indefinitely just as patients with high blood pressure or diabetes require lifelong therapy.

### **64. Should I have another MRI of the brain or spinal cord if my disease is not controlled?**

Obtaining periodic MRI scans can be very useful in monitoring the disease and response to therapy. There is no consensus on how often MRI scans should be obtained, but annually for the first couple of years after starting therapy may be useful. Further scans can be obtained as needed. The MRI scan usually includes the brain only but can also include the spinal cord as needed.

### **65. Are there any interactions between the DMT and other drugs commonly used in MS?**

The interactions between DMTs and other drugs used in MS have not been fully evaluated. However, results from controlled trials of the DMTs did not suggest any significant interaction with commonly used therapies in MS.

### **66. What if my insurance does not cover the DMT or what if I have no insurance?**

DMT are expensive and may cost \$15,000 to \$23,000 per year. However, all these drugs are FDA approved for RRMS and most insurance companies will cover them. The amount covered and the patient's out of pocket co-pay, however, may vary from one insurance plan to another. Each insurance plan has a different deductible and co-pay that the patient needs to know about.

If the patient has no insurance or inadequate insurance coverage, the drug companies that make these DMTs have patient assistance programs which can provide these patients with free or reduced-cost therapy. Furthermore, there may be federal or state funded programs that may cover the cost of these medications.