Disease modifying drug therapy

Multiple Sclerosis Trust

MS

New edition for 2014 - 15

We hope you find the information in this book helpful. If you would like to speak with someone about any aspect of MS, contact the MS Trust information team and they will help find answers to your questions.

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Introduction

This book is for people with relapsing MS who are considering treatment with one of the disease modifying drugs. The aim is to provide an understanding of how the available drugs work, how they affect MS and help readers have informed discussions with a neurologist or MS specialist nurse about the treatment options. The book will be used in different ways by different people, depending on the time since their diagnosis, the nature of their MS and their previous treatment history. The book is not intended as a substitute for clinical advice.

The decision to start disease modifying treatment should be made in partnership between the individual and their MS team. Ideally this discussion should happen soon after diagnosis, even if the decision is not to start treatment immediately. The discussion will need to consider factors such as the benefits and risks of starting or delaying treatment, the benefits and risks of the different drugs and how treatment might affect other areas of a person's life.

The management of MS is a rapidly changing environment. Recent progress has seen new disease modifying therapies being investigated in clinical trials which may change the treatment options for people with MS in the future. This book aims to keep people up to date on the disease modifying drugs that are currently available for MS to support them in the choices that they may need to make.

The book is divided into three main sections. The first discusses what the disease modifying drugs do and how they are used; the second looks at the drugs that are currently approved for the treatment of MS; the third section includes ideas for questions to ask a neurologist or MS specialist nurse.

What is MS?

Multiple sclerosis is considered to be an autoimmune condition, whereby the immune system attacks the body's tissue, causing inflammation and damage. In MS, the immune system attacks myelin - the fatty protein that forms a sheath around nerve cells in the central nervous system (the brain and the spinal cord). This causes inflammation and damage to the myelin (called demyelination), which disrupts the way in which nerve messages are carried to and from the brain, leading to the symptoms of MS.

In the early stages of MS, it is possible for the body to repair damaged myelin (remyelination), or the central nervous system may re-route messages via different nerve pathways thereby avoiding damaged areas. However, if the nerves are left without the protection of myelin or the area of damage becomes too large, nerve fibres will be permanently destroyed and messages in that part of the central nervous system may become permanently blocked.

What are the different types of MS?

Whilst MS does not follow a set pattern, varying from person to person, there are some broad types.

Relapsing remitting

Most people are diagnosed with relapsing remitting MS. A relapse is the onset of symptoms or disability lasting at least 24 hours but, more commonly, for a number of days or weeks. The number of relapses someone experiences will vary. Typically, people will experience one or two relapses a year, followed by a period of good or complete recovery (remission). There is a tendency for recovery to become less complete over time and each relapse may leave more permanent symptoms or disability in some people.

If the rate and severity of relapses has not been controlled by treatment with one of the disease modifying drugs, this is referred to as **highly active** relapsing remitting MS.

If someone has two or more severe, or disabling, relapses in a year and shows areas of new damage (lesions) on two consecutive MRI (magnetic resonance imaging) scans, this can be referred to as **rapidly evolving severe** relapsing remitting MS (RES).

Secondary progressive

Many people initially diagnosed with relapsing remitting MS find that over time, often many years, the frequency of relapses decreases and eventually stops but disability gradually increases.

Primary progressive

About 10% of people will be diagnosed with primary progressive MS in which disability increases from the outset with few or no relapses.

Clinically isolated syndrome (CIS)

Clinically isolated syndrome (CIS) is an individual's first episode of neurological symptoms lasting at least 24 hours but from which it is not possible to diagnose a definite cause. For some it may be the first attack of what turns out to be MS, although not everyone who experiences a CIS will go on to develop MS and for some there may be no further symptoms.

What are disease modifying drugs?

Disease modifying drugs work by interacting with different parts of the immune system to calm down the inflammation that causes MS relapses. All of these drugs principally affect the relapse rate, and have not been proven to have any beneficial effect for people who are not having relapses.

There are currently ten disease modifying drugs approved in the UK for some of the relapsing forms of MS. These drugs can only be prescribed by a neurologist.

Disease modifying drugs are not a cure for MS. They reduce the number and severity of relapses rather than always stopping them entirely. Some clinical trials have claimed that, through the reduction in relapses, some of the drugs slow the build-up of disability, but this is not fully established. In particular, it is not clear whether any of the drugs will reduce the build-up of disability over the longer term.

Some research suggests that benefits are greater with early treatment, effectively before someone is showing signs of disability, and may reduce the build up of damage to nerve cells. If someone has only had a couple of relapses and has few or very mild symptoms, the decision to start long-term treatment early will be a difficult one. Individual neurologists will have their own guidance when it comes to the appropriate time to start, but they should be willing to discuss treatment options with the person.

When used in people with clinically isolated syndrome, some of the disease modifying drugs may increase the time between the first onset of symptoms and further attacks that lead to a definite diagnosis of MS. However, as not all people who have clinically isolated syndrome will be diagnosed with MS, the neurologist may be reluctant to start what may be an unnecessary treatment too early.

It is important to recognise that while these drugs are a long-term commitment, they are not necessarily a lifelong commitment. While they may prove effective over a longer period, they may not maintain the same level of effectiveness, as the type of MS changes. A neurologist will regularly review treatment and advise when switching, or stopping treatment altogether, needs to be considered.

Whilst the effectiveness of these drugs has been demonstrated, it is important to remember that every individual's experience is unique. A drug that is suitable and effective for one person may not be right for another. Some will do better than expected, whilst others might not do as well.

When is the right time to start disease modifying treatment?

The decision to start disease modifying treatment is very personal. It may involve both health related factors such as the impact of relapses on daily life, and also lifestyle issues, such as the storage and transport of the drugs, or the need for regular visits to the clinic. The emotional effect of starting on long-term treatment, particularly if someone feels quite well, may also be an important factor.

A neurologist or MS specialist nurse will help when discussing which treatment is most suited to an individual. This might take into consideration how MS affects them, their lifestyle, how treatment might be managed over a long period and expectations of effectiveness.

Some people will choose not to start disease modifying treatment. There are also benefits and risks associated with this approach which need to be discussed with the neurologist or MS specialist nurse, ensuring that whatever individual decision is made, it is an informed choice.

What are the benefits and risks of disease modifying treatment?

The benefits and risks of each of the treatment choices should form part of the discussion with the MS team. Perceptions of what constitutes a benefit or a risk will vary. Some people may consider the convenience of taking a particular drug a benefit, whilst others may be more focussed on the degree to which the drug reduces the number of relapses.

Whilst some people report that symptoms of MS, such as fatigue or pain, improve when taking disease modifying drugs, this is probably a result of the effect on inflammation. For most people, the benefits of treatment are not immediately obvious; they may

continue to have a background of symptoms and may find it difficult to make a direct comparison between taking or not taking a drug. There may be times when a person feels that the treatment is not working and they may feel tempted to stop. This may particularly be the case if they are experiencing side effects that mean they actually feel worse than they did before starting treatment.

All medicines can potentially cause side effects. Some disease modifying drugs have been in use since the 1990s and their side effects are considered to be relatively mild and manageable, often easing over time as the body adapts. However, some people may find the side effects inconvenient and intrusive enough to change or stop treatment.

More recent disease modifying drugs have a greater effect on the relapse rate, but have more marked, and potentially serious, side effects. Although there are mechanisms in place to monitor people taking these drugs, and intervene quickly should problems arise, some people will feel that this is a risk they are unwilling to take. Others may feel that the benefits of these treatments outweigh the risks.

Further details of the benefits and risks of individual drugs are given in section 2.

Can treatment continue during pregnancy or breastfeeding?

If a woman is considering starting a family, she will need to discuss this with a neurologist as she may need to delay, or have a break from, treatment. Disease modifying drugs have not been studied in pregnant or breastfeeding women and there is limited information available. As the effect on the child is unknown, women are usually advised to stop treatment until they have finished breastfeeding. If a woman becomes pregnant

whilst taking one of the drugs, she will be informed of potential risks, and stopping treatment during the pregnancy should be considered.

Whilst treatment is not contraindicated for a man who is planning to start a family, these plans may also need to be discussed with a neurologist or MS specialist nurse. Currently, there is very limited data concerning the impact of disease modifying therapies on conception or foetal development when the potential father is taking medication.

2. Disease modifying drugs for MS

This section of the book will explain further the eligibility criteria for each of the disease modifying drugs, how they can help with MS and how treatment might be given.

In the UK, there are a number of disease modifying drugs that have been approved for use on the NHS for people with different degrees of relapsing MS or clinically isolated syndrome:

- interferon beta 1a (Avonex and Rebif)
- interferon beta 1b (Betaferon and Extavia)
- glatiramer acetate (Copaxone)
- teriflunomide (Aubagio)
- dimethyl fumarate (Tecfidera)
- fingolimod (Gilenya)
- natalizumab (Tysabri)
- alemtuzumab (Lemtrada)

(Brand names of the drugs are shown in brackets).

A neurologist or MS specialist nurse will talk about treatment options or eligibility for treatment, and provide guidance on what might be the right choice for an individual.

Every effort has been made to ensure that the information in this book is accurate and up to date (October 2014). However, this is a rapidly developing aspect of MS treatment with regular changes to NHS eligibility for existing drugs and approval of new treatments.

The online version of this book will be updated as eligibility criteria are amended or new disease modifying drugs become available. See www.mstrust.org.uk/dmts for the most up to date information.

Beta interferon and glatiramer acetate

Who is eligible for treatment?

Beta interferon drugs and glatiramer acetate have been available on the NHS since approximately 2002.

The prescribing criteria for the beta interferon drugs and glatiramer acetate are based on guidelines from the Association of British Neurologists (ABN). People who meet the criteria are entitled to treatment on the NHS.

Prescribing criteria

- a maximum Expanded Disability Status Scale (EDSS) score 6.5 - that is, able to walk (with or without walking aids) about 10 metres without resting
- have experienced at least two clinically significant relapses in the last two years OR a single major relapse in the preceding two years, with MRI scan suggesting active MS
- normally be aged 18 or above.

The neurologist may also consider treatment with a beta interferon drug when an MRI scan indicates a high likelihood of developing MS within 12 months of a clinically isolated syndrome.

Assessment before treatment

Blood tests will be taken before treatment is started to check for problems that might affect how well a person will do on the drugs. The neurologist needs to be made aware of any pre-existing conditions or reactions to previous treatments. Whilst treatment may still be an option, it may need to be started in a different way.

How do these drugs work for MS?

Beta interferon

Interferons are proteins produced naturally in the body which alter how the immune system responds to infection. Beta interferon reduces both the immune response and inflammation. In MS, the

immune system attacks the body's own myelin; beta interferon can help to reduce this immune response.

There are two forms of beta interferon used for the treatment of MS:

- interferon beta 1a (Avonex and Rebif)
- interferon beta 1b (Betaferon and Extavia).

The differences between these forms lie in the way they are manufactured.

Glatiramer acetate

Glatiramer acetate (Copaxone) produces similar results to beta interferon but acts in a different way. Glatiramer acetate is a synthetic combination of four amino acids, resembling the myelin protein surrounding nerve fibres. It is thought to lessen the immune reaction that attacks myelin.

How are beta interferon or glatiramer acetate given?

These are injected, either under the skin (subcutaneous) or into a muscle (intramuscular).

Drug	Frequency	Where injected
Avonex (interferon beta 1a)	once a week	into a muscle
Betaferon (interferon beta 1b)	every other day	under the skin
Extavia (interferon beta 1b)	every other day	under the skin
Rebif (interferon beta 1a)	three times a week	under the skin
Copaxone (glatiramer acetate)	every day	under the skin

All of these drugs come with devices to make injection easier. Many people may feel nervous about filling or holding a needle and seeing the needle going into the skin. Some devices help with this.

The first dose of the drug is usually given in the presence of a nurse, who will give instructions on the injection technique. The nurse will discuss the practicalities and offer advice or training and ongoing support if necessary.

Drug companies provide homecare support allowing drugs to be delivered direct to an individual's home, so they do not need to be obtained from a pharmacist. They also give advice on drug storage, travelling with the drug, safety issues of medicines in the home and disposal of sharp needles.

Benefits of beta interferon and glatiramer acetate

Beta interferon and glatiramer acetate have been used to treat MS since the 1990s. In clinical trials these drugs reduced the frequency of relapses by around one third. MRI scans showed most people were found to have fewer, smaller or no new areas of damage within the central nervous system. Beta interferon may also reduce the severity of relapses.

By limiting lesion formation, beta interferon may also delay or slow disability, particularly when treatment is started early in the disease course. However, there is a lack of clarity about the extent of the effect on disability.

In addition, beta interferon and glatiramer acetate have been shown, in clinical trials, to delay the conversion from clinically isolated syndrome to clinically definite MS in the two to five years following the start of treatment.

Side effects of beta interferon or glatiramer acetate

For most people, any side effects of these drugs are relatively mild and manageable.

Beta interferon

One of the more common side effects of beta interferon is flu-like symptoms, such as headache, muscle ache and stiffness, chills or fever, which may occur following injection and may lessen over time. Injection into a muscle may also produce discomfort and stiffness.

An MS specialist nurse will provide support and ensure any side effects experienced are managed as effectively as possible. There are various strategies that may be recommended to reduce the risk of experiencing side effects. For example:

- a lower dose may be given at the start of treatment and the dose will be slowly increased over time to allow the body to adjust to the drug
- to help with flu-like symptoms, it may be helpful to change the time of day of injection in order to sleep through the worst of the side effects
- to help reduce body temperature, paracetamol or ibuprofen can be taken before the injection and at four to six hour intervals after the injection, as required.

Glatiramer acetate

Some people may experience a reaction, known as the Immediate Post-Injection Reaction (IPIR), which can occur immediately after injection. This may involve one or more of the following: flushing, tightness of the chest, shortness of breath and palpitations. This reaction can last 15-30 minutes and will ease without any treatment.

Side effects of beta interferon and glatiramer acetate

Treatment	Common (affect more than 1 person in 100)	Less Common (affect fewer than 1 person in 100)
beta interferon (Avonex Betaferon Extavia Rebif)	• flu-like symptoms • headache • injection site reactions • blood cell abnormalities • feeling weak or tired • difficulty sleeping • diarrhoea, nausea and vomiting • muscular or joint pain • infections	• changes in menstruation (periods) • neurological symptoms, mood changes, depression • liver abnormalities • allergic reactions • heart problems and hypertension • alopecia • damage to small blood vessels leading to kidney problems
glatiramer acetate (Copaxone)	• injection site reactions • lipoatrophy (indentations in the skin) • headache • depression, anxiety • nausea • feeling weak • chest pain, pain • swollen lymph nodes • gastrointestinal changes	• blood cell changes • extra heartbeats • thyroid changes • dilation of blood vessels • immediate post-injection reaction (IPIR)

Assessment during treatment

If the neurologist prescribes one of the beta interferon drugs, blood tests will be performed regularly throughout treatment to check that the body is tolerating the drug. Regular blood tests may be taken during the first year of treatment and, assuming a person responds well, may be reduced to once a year, although this may vary between centres. Treatment with glatiramer acetate does not require regular blood tests.

Assessments will be made to monitor how the person's MS is responding to treatment. This may involve checking body functions such as vision, strength, sensation, thinking and activity performance.

Neutralising antibodies

Antibodies are proteins produced by the immune system to fight foreign substances, such as infection. Sometimes the body's natural defences will develop antibodies against drugs entering the body, 'neutralising' their effect.

Treatment with beta interferon drugs can lead to the development of neutralising antibodies (NAbs), which can reduce their effectiveness. The person may experience a similar number of relapses as they would have done before taking the drug, or develop new MS lesions that are detected using MRI. Neutralising antibodies are not associated with any new side effects or long-term safety issues.

The majority of people will not develop significant levels of neutralising antibodies and in some people they may reduce again over time. A test may be performed if the presence of neutralising antibodies is suspected. Depending on the results, the neurologist may then discuss whether to continue with treatment, or suggest switching to a disease modifying treatment that is not beta interferon.

Teriflunomide (Aubagio)

Who is eligible for treatment?

Teriflunomide (Aubagio) was approved for use on the NHS in 2014.

The drug can be prescribed for adults with active relapsing MS. Active MS is generally defined as having two relapses which have had a substantial effect on health or daily life in the last two years. NHS approval excludes people who have highly active or rapidly evolving severe relapsing remitting MS (see page 6 for explanations of these types of relapsing remitting MS).

Assessment before treatment

Before treatment, blood samples will be taken to check liver function and to measure blood cell counts. Blood pressure will also be checked.

Treatment with teriflunomide should not be started by women who are pregnant, breastfeeding or are planning to become pregnant in the near future.

Treatment with teriflunomide may not be appropriate for people with severe liver problems, serious problems affecting the immune system (eg AIDS) and significant problems affecting bone marrow or reduced blood cell counts (eg anaemia, leucopenia, neutropenia or thrombocytopenia).

Start of treatment may be delayed if there are signs of a serious infection.

How does teriflunomide work?

The mechanism of action of teriflunomide is not completely understood but it is thought that the main effect is to stop certain

immune cells from multiplying.

This results in lower numbers of both B-cells and T-cells, two types of white blood cells involved in the immune response associated with MS.

How is teriflunomide given?

Teriflunomide is taken by mouth as a tablet, once daily.

Benefits of teriflunomide

Clinical studies have shown that teriflunomide reduces the number of relapses by approximately one third and delays the rate of disease progression by about one third.

Side effects of teriflunomide

A common side effect of treatment includes increased liver enzyme levels, indicating liver damage. In addition, nausea, diarrhoea, and hair thinning can occur during the first few months of treatment but generally improve in the following months of treatment.

Side effects of teriflunomide

Common (affect more than 1 person in 100)	**Less Common** (affect fewer than 1 person in 100)
• increased levels of liver enzymes • nausea • diarrhoea • hair thinning (alopecia) • urinary tract infection • inflammation of the nose and throat • influenza • pins and needles • infections • decrease in white blood cells (neutropenia) • mild allergic reactions • anxiety • nerve pain • peripheral neuropathy • increase in blood pressure • rash • musculoskeletal pain	• decrease in red blood cells (anaemia) • decrease in blood platelets (thrombocytopenia)

Contraception and pregnancy

Based on data in animal studies, there is an increased risk of having a baby with birth defects if teriflunomide is taken during pregnancy. Teriflunomide remains in the blood for a long time after stopping treatment, so this risk may continue for up to two years.

Women of childbearing age must use an effective method of contraception during treatment and for two years after stopping teriflunomide.

Women who suspect that they are pregnant while taking teriflunomide, or in the two years after stopping treatment, should contact their GP immediately for a pregnancy test. If the test confirms pregnancy, the blood level of teriflunomide can be reduced rapidly to safe levels by taking certain medicines (cholestyramine or activated charcoal).

Women who wish to become pregnant should stop taking teriflunomide. The removal of teriflunomide can be speeded up using the medicines described above. A blood test can confirm that levels of teriflunomide are low enough that it is safe to attempt to become pregnant.

Assessment during treatment

Blood tests should be performed to monitor changes in liver function, generally every 2 weeks for the first 6 months and every eight weeks thereafter.

Blood pressure and blood cell counts will also be monitored periodically during treatment.

Neutralising antibodies

Based on the chemical nature of teriflunomide, treatment is unlikely to increase the risk of developing neutralising antibodies. However, as teriflunomide is a new medicine with comparatively less data in the clinical setting than other disease modifying therapies, there is currently no information to be had on this risk.

Dimethyl fumarate (Tecfidera)

Who is eligible for treatment?

Dimethyl fumarate was approved for use on the NHS in 2014.

In England, Wales and Northern Ireland, the drug can be prescribed for adults with active relapsing remitting MS. Active MS is generally defined as having two relapses which have had a substantial effect on health or daily life in the last two years. NHS approval excludes people who have highly active or rapidly evolving severe relapsing remitting MS (see page 6 for explanations of these types of relapsing remitting MS).

In Scotland, dimethyl fumarate is approved for adults with relapsing remitting MS.

Assessment before treatment

Before treatment, blood and urine tests will be carried out to measure blood cell counts and to check liver and kidney function.

How does dimethyl fumarate work?

The mechanism of action of dimethyl fumarate is not completely understood but it is thought that it reduces inflammation caused when the immune system attacks myelin, resulting in less damage to myelin. Dimethyl fumarate may also have neuroprotective properties, preventing damage to nerve cells caused by chemicals released during the immune attack.

How is dimethyl fumarate given?

Dimethyl fumarate is taken by mouth as a capsule, twice a day, with food.

To minimise the impact of side effects, a lower starting dose is recommended for the first week of treatment, increasing to a full dose in the second week.

Benefits of dimethyl fumarate

Clinical studies have shown that dimethyl fumarate reduces the number of relapses by approximately 50%. MRI scans showed most people had fewer, smaller or no new areas of active MS within the central nervous system during the two year study.

Dimethyl fumarate may also slow down the build-up of disability associated with MS; in one large scale study which measured disability over a two year period, people taking dimethyl fumarate were less likely to experience worsening of their disability compared to those taking placebo.

Side effects of dimethyl fumarate

Common (affect more than 1 person in 100)	**Less common** (affect fewer than 1 person in 100)
• flushing and feeling hot • gastrointestinal upset (nausea, diarrhoea, abdominal pain, vomiting, indigestion) • decrease in white blood cells • rash • increased levels of liver enzymes • changes in kidney function	

The most common side effects include:

- flushing and feeling hot
- gastrointestinal upset – diarrhoea, nausea, abdominal pain.

People are more likely to have these side effects when they first start taking dimethyl fumarate (mostly during the first month). Most people have mild to moderate symptoms which tend to go away over time.

The impact of side effects can be reduced by starting on a low dose of 120mg tablet twice daily, for one week, increasing to 240mg tablet twice daily in the second week.

A neurologist or MS specialist nurse may suggest ways to further reduce these side effects. Various strategies may be recommended including:

- temporary dose reduction, returning to full dose within one month
- taking aspirin before each dose to prevent flushing
- taking doses on a full stomach to reduce gastrointestinal upset – experience suggests this needs to be a balanced meal rather than a light snack.

In addition, in clinical trials changes in liver and kidney function were reported. Regular blood and urine tests are recommended to monitor for possible effects.

Assessment during treatment

Blood and urine tests should be carried out at three and six months after starting treatment and then every six to twelve months to monitor blood cell counts and liver and kidney function. Depending on local practise, tests may be carried out

at a local GP surgery or it may be necessary to attend a hospital clinic.

Neutralising antibodies

Based on the chemical nature of dimethyl fumarate, treatment is unlikely to result in the generation of neutralising antibodies. However, as dimethyl fumarate is a new medicine with comparatively less data in the clinical setting than other disease modifying therapies, there is currently no information to be had on this risk.

Fingolimod (Gilenya)

Who is eligible for treatment?

Fingolimod (Gilenya) has been approved for use on the NHS since 2012.

Across the UK, fingolimod can be prescribed for people with highly active relapsing remitting MS, that is those people who continue to have relapses despite treatment with one of the beta interferon drugs for at least one year.

In England and Scotland, fingolimod approval has been extended to include additional groups.

In England, fingolimod can also be prescribed for people with high disease activity despite treatment with glatiramer acetate and for people taking natalizumab who are at high risk of developing PML.

In Scotland, fingolimod can also be prescribed for people who have high disease activity despite treatment with at least one disease modifying therapy and additionally for people with rapidly evolving severe relapsing remitting MS (two or more disabling relapses in one year and MRI evidence of new areas of MS activity).

See page 6 for explanations of highly active and rapidly evolving severe relapsing remitting MS.

Assessment before treatment

Before treatment, additional tests will be carried out to check for immunity against the virus that causes chicken pox and to measure blood pressure and pulse.

Certain conditions, such as liver disease and heart problems, will require a medical assessment before fingolimod is prescribed and may require monitoring during treatment. Some situations may rule out treatment with fingolimod, these include a current malignancy (except for a certain type of skin cancer), where there

is a greater risk of opportunistic infections, people with a history of cardiac problems, certain conditions affecting blood supply to the brain or treatment with medications which slow heart rate.

How does fingolimod work?

Fingolimod works by binding to the surface of white blood cells in the immune system, trapping them in the lymph nodes and preventing them from attacking cells in the central nervous system.

How is fingolimod given?

Fingolimod is taken once daily, by mouth, in capsule form. The first dose is given in a hospital or clinic and is overseen by a neurologist or MS specialist nurse as fingolimod is known to affect heart rate and blood pressure. These symptoms are monitored for at least six hours (sometimes for longer), for any irregularity, which may involve the use of a continual electrocardiogram (ECG) monitor.

Any irregular heartbeat should return to normal in a day, and changes in heart rate should return to normal within the first month.

Unless there are problems that require further monitoring, after the first dose, fingolimod can be taken without supervision at home, with routine health reviews at the clinic.

The benefits of fingolimod in MS

Studies from clinical trials have shown that fingolimod reduces the number of relapses by approximately a half and delays the rate of disease progression by a third. The drug may also reduce the development of new MS lesions detected using MRI.

Side effects of fingolimod

The most common side effects of treatment include increased risk of infections, cough, headache, back pain and diarrhoea.

Side effects of fingolimod

Common (affect more than 1 person in 100)	**Less common** (affect fewer than 1 person in 100)
• headache • back pain • diarrhoea • cough • raised liver enzyme levels • infections: herpes virus, fungal, flu • changes in heartbeat • nausea, vomiting • cough with phlegm, chest discomfort, sinusitis, worsening of existing severe lung problems • dizziness, weakness • tingling or numbness • lowering of white blood cells • skin rash, itching • depression • eye pain, blurred vision • mild increase in blood pressure • elevations in certain blood lipids	• pneumonia • macular oedema (swelling in the back of the eye) • low mood • lowering of neutrophils (type of white blood cell) • risk of cancer

Assessment during treatment

Treatment with fingolimod will require health monitoring regularly during the first year; less often in subsequent years. This will involve an evaluation of how the person has responded to treatment, as well as blood pressure and liver function tests.

Certain pre-existing conditions that affect the eye, for example diabetes, may require that an ophthalmologist gives a regular eye examination throughout treatment, as fingolimod treatment may increase the risk of developing macular oedema (swelling in the back of the eye). Only one ophthalmological exam is recommended for all other individuals after three to four months of treatment. In addition, people are advised to talk to a doctor if any changes or visual disturbances are noticed.

Neutralising antibodies

Based on the chemical nature of fingolimod, treatment is unlikely to increase the risk of developing neutralising antibodies. However, as fingolimod is a new medicine with comparatively less data in the clinical setting than other disease modifying therapies, there is currently no information to be had on this risk.

Natalizumab (Tysabri)

Who is eligible for treatment?

Natalizumab (Tysabri) has been approved for use on the NHS since 2007.

It can be prescribed for people with rapidly evolving severe relapsing remitting MS, that is people who experience two or more disabling relapses in one year, with signs of increasing or new lesions between two consecutive MRI scans.

Before starting treatment, a neurologist will discuss benefits and risks of treatment and a risk education session may be offered. Consideration needs to be given to how treatment will fit with lifestyle, for example the importance of attending appointments every four weeks for infusion. The dose and frequency of administration of natalizumab is to ensure optimum levels of the drug remain in the body at all times, so it is important a dose is not missed. The effects of treatment may start to wear off after about six weeks of stopping.

Assessment before treatment

Blood tests may be performed before treatment commences to determine whether it is safe to receive natalizumab. Assessment of liver function may also form part of this.

The neurologist needs to be informed of any pre-existing conditions, prior exposure to immunosuppressants (for example mitoxantrone, azathioprine) or any reaction to previous drugs or treatments, at this time.

How does natalizumab work?

Natalizumab binds to cells in the immune system, stopping them passing from the blood into the central nervous system where they can damage nerves.

How is natalizumab given?

Natalizumab is given as an intravenous infusion (a small tube placed in a vein, with the treatment infused via a pump) once every four weeks. The drug is generally administered in an infusion clinic, under

the supervision of a qualified health professional.

Prior to each infusion, blood pressure, temperature and pulse rate will be taken. The infusion usually takes one hour. Monitoring will also take place during the infusion and for one hour after, to check for any serious allergic reaction (hypersensitivity).

Benefits of natalizumab

In clinical trials, natalizumab was shown to reduce the relapse rate by 67% in people with relapsing remitting MS. Experience in clinical practice suggests natalizumab may decrease the number of relapses by 81%, reduce the rate of disease progression by approximately two thirds and the accumulation of new MS lesions that are detected using MRI.

Side effects of natalizumab

Commonly reported side effects of natalizumab include dizziness, nausea, urticaria (a skin rash), stiffness and an increased chance of infection. Natalizumab may affect liver function and this will be monitored during treatment. Liver function generally recovers when treatment is stopped.

Common (affect more than 1 person in 100)	**Less common** (affect fewer than 1 person in 100)
• urinary tract infections • inflammation of the nose and throat • shivering • urticaria (itchy skin rash) • headache • dizziness • nausea, vomiting • stiffness, joint pain • fever • fatigue	• severe allergic reaction during infusion (rash, swelling of face, lips or tongue, difficulty breathing) • discomfort during the infusion including nausea, headache, or dizziness • progressive multifocal leukoencephalopathy (PML) • serious infection • liver problems

PML

Treatment with natalizumab may increase the risk of progressive multifocal leukoencephalopathy (PML), an uncommon brain infection that can lead to severe disability or even death. PML is caused by a mutation of the JC virus, which is present in about half of the population and normally kept under control by the immune system. If the function of the immune system is weakened and the body is less able to fight an infection, which may occur with natalizumab, the virus can cause inflammation and damage to the brain.

There is a blood test that can be used to detect the JC virus and helps to identify risk of PML. Other factors which increase the risk of PML include prior treatment with an immunosuppressant drug (for example azathioprine, cyclophosphamide, mitoxantrone or methotrexate) and the length of time a person has been receiving natalizumab. The neurologist or MS specialist nurse will discuss the implications of the blood test and how it may affect the benefits and risks of treatment.

People receiving natalizumab will be informed of the early signs and symptoms of PML. These can be similar to an MS relapse, so it is important to report any new or worsening symptoms. If PML is suspected at any point during treatment, the drug will be discontinued immediately.

As the risk of developing PML may change with time, natalizumab treatment is part of an ongoing safety programme which closely monitors and assesses the risk that people being treated with the drug have for developing PML. The risk of developing PML is considered relatively small.

Due to the potential risk of side effects, a patient alert card should be issued with the drug, containing important safety information needed before and during treatment.

Assessment during treatment

Blood tests may be performed during treatment as part of the monitoring process. Annual blood samples may be taken to monitor changes in liver function, the development of neutralising antibodies to the drug and the JC virus.

It is important to discuss any MS relapses during treatment with the neurologist. If the rate and severity of relapses does not improve after six months of treatment, the neurologist will need to consider whether treatment should continue.

Neutralising antibodies

Treatment with natalizumab can lead to the development of neutralising antibodies (NAbs). If these neutralising antibodies persist, they may reduce the benefit from treatment and may increase the chance of developing serious allergic (hypersensitivity) reactions.

Most people will not develop neutralising antibodies and in some people they may disappear again over time. A test may be performed if the presence of neutralising antibodies is suspected. A further confirmatory test will be repeated after six weeks. If the neutralising antibodies continue to be present, treatment may have to be discontinued.

Alemtuzumab (Lemtrada)

Who is eligible for treatment?

Alemtuzumab (Lemtrada) was approved for use on the NHS in 2014.

The drug can be prescribed for adults with active relapsing remitting MS. Active MS is generally defined as having two clinically significant relapses in the previous two years. In practice, this means two relapses which have had a substantial effect on health or daily life in the last two years.

Assessment before treatment

Before treatment, blood and urine tests will be carried out to measure blood cell counts and to check the function of the thyroid gland and kidneys. People who have no history of chickenpox infection should be tested for exposure and vaccination given to anyone who may be susceptible.

How does alemtuzumab work?

Alemtuzumab works by binding to and killing immune cells (lymphocytes or white blood cells) which are involved when the immune system attacks myelin. It is thought that the cells which grow back after treatment do not cause damage to nerves.

How is alemtuzumab given?

Alemtuzumab is given as two treatment courses of intravenous (iv) infusions.

- the first course of treatment consists of iv infusions over five consecutive days
- the second course of treatment is taken 12 months later and consists of iv infusions over three consecutive days.

In some centres, these courses are administered with people attending each day as outpatients. Other centres may admit people as hospital inpatients for the duration of the treatment course.

Most of the people who took alemtuzumab in large scale studies did not require additional treatment courses during the two year investigations. On-going studies are monitoring the requirement for retreatment in subsequent years.

Benefits of alemtuzumab

In clinical trials, alemtuzumab reduced the number of relapses by approximately 70%. Relapse severity was also reduced. MRI scans showed most people had fewer, smaller or no new areas of damage within the central nervous system.

Alemtuzumab may also slow down the build-up of disability associated with MS; in one large scale study which measured disability over a two year period, people taking alemtuzumab were less likely to experience worsening of their disability compared to those taking beta interferon.

Side effects of alemtuzumab

Common (affect more than 1 person in 100)	**Less common** (affect fewer than 1 person in 100)
• overactive or underactive thyroid • infusion associated reactions including headaches, rashes, fever and nausea • infections – respiratory and urinary • decrease in white blood cells (lymphopenia) • pins and needles • changes in blood pressure, heart rate • rash • musculoskeletal pain	• idiopathic thrombocytopenic purpura (ITP), a serious blood clotting disorder • kidney problems • increased levels of liver enzymes

Three serious side effects have been reported from clinical trials.

- overactive or underactive thyroid gland leading to thyroid disorders
- idiopathic thrombocytopenic purpura (ITP), a serious disorder which prevents blood from clotting
- kidney problems

These side effects are potentially serious but are treatable if caught early enough. People taking alemtuzumab will be informed of the early signs and symptoms of these side effects.

To ensure early detection of side effects, it is vital that anyone treated with alemtuzumab continues to have monthly blood and urine tests for four years after the last course of treatment. Depending on local practise, tests may be carried out at a local GP surgery or it may be necessary to attend a hospital clinic.

Other common side effects include:

- infusion-related reactions such as headache, rashes, fever and nausea. Most people treated with alemtuzumab are affected by these reactions but they are generally mild to moderate and short-lived. To minimise infusion-related reactions, additional medications are given before infusions
- infections including coughs, colds, chest infections and herpes virus infections (such as cold sores or shingles). As alemtuzumab works by suppressing the immune system, for some time after the infusion people will be more vulnerable to infections such as colds and viruses. To reduce the risk of herpes infections, an antiviral medication should be taken starting from the first day of infusion and continued for at least one month.

Assessment during treatment

Because of the serious nature of the potential side effects, it is vital that monthly blood and urine tests are carried out for four years after the last infusion to monitor blood cell counts and to check the function of the thyroid gland and kidneys.

Neutralising antibodies

Based on the treatment schedule of alemtuzumab, treatment is unlikely to result in the generation of neutralising antibodies. However, as alemtuzumab is a new medicine with comparatively less data in the clinical setting than other disease modifying therapies, there is currently no information to be had on this risk.

Switching or stopping treatment

There are two main reasons why people might switch from one disease modifying drug to another, or discontinue treatment altogether:

- lack of effectiveness
- unmanageable side effects

Switching treatment

It is important to have realistic expectations about the drugs and what they might achieve. All of these drugs take several months to start working and show benefit in reducing the number of relapses. After starting treatment, relapses may stop altogether or still occur but at a reduced rate. However, if after a period of time there is no obvious improvement, or the number and severity of relapses remains as it was before treatment, switching to another disease modifying drug may be an option.

A small number of people find that the side effects of a particular drug are unmanageable and do not improve or resolve over time. Some people may develop persisting high levels of neutralising antibodies. Again, switching to another drug may be a possibility.

The neurologist and MS specialist nurse will advise on eligibility and suitability for alternative treatments. Switching may involve a short ‘drug holiday’, to make sure that the previous treatment has been flushed from the body before starting the new drug.

Stopping treatment

Some people who find the drugs ineffective, or the side effects unmanageable, may choose to stop treatment. Even if the drugs have been effective in the past, there may come a time when the nature of the MS changes and treatment is no longer effective.

A proportion of people diagnosed with relapsing remitting MS will eventually find that they develop secondary progressive MS, meaning they have fewer relapses but have a gradual increase in disability. People with secondary progressive MS who continue to experience relapses may be kept on an appropriate disease modifying drug.

Progressive forms of MS are thought to be caused by permanent degeneration to the nerves, rather than new episodes of inflammation. Clinical trials of disease modifying drugs have not shown benefit in people with progressive forms of MS where relapses do not occur. As there are currently no disease modifying drugs that are effective in progressive MS, the focus of treatment is on managing the specific symptoms that someone may experience.

The neurologist and MS specialist nurse will discuss the reasons why treatment may need to be stopped and give advice on an appropriate time to do this. Stopping treatment can be emotionally difficult, but the neurologist and MS specialist nurse will give support throughout the process.

If the chosen drug treatment is proving to be of benefit and the side effects manageable, there will be no reason to switch, or stop, treatment.

3. Tips for discussing disease modifying drug therapy

To get the most from discussions with a neurologist or MS specialist nurse, it is helpful to prepare in advance.

Useful consultation tips

- Before your appointment, make a list of the questions you want to ask. List these in order of importance in case time runs out.
- Some people feel it useful to take someone with them who understands their situation and can be both supportive and help organise information.
- During the consultation, try not to feel pressurised or rushed.
- Ask about any follow up appointments that may be necessary.
- If you feel the appointment was rushed, ask for another one to discuss any questions or concerns further.
- Ask for clarification of anything that has not been fully understood. Note down key points from the discussion to help remember everything and ease what may be an uncomfortable situation.
- Discuss any feelings or concerns about a treatment and the impact it may have on daily life. Check whether there is a leaflet, or other material, explaining treatments or tests.
- In some cases, the neurologist you are seeing may not be an expert in MS and you may need to be referred on to an MS specialist for treatment.
- Feel free to ask for specific reasons why the neurologist does not think a treatment is suitable for you. If you wish, you could ask them to refer you for a second opinion to another neurologist (often in the same hospital). Most will be willing to arrange this.

Example questions to ask

Drug treatment:

- Why should I consider taking disease modifying drugs?
- How soon should I be thinking about starting disease modifying treatment?
- What drugs are currently appropriate for me and how effective are they?
- Is there information about long-term use of these drugs?
- Are there many side effects associated with the disease modifying drugs?
- Does the treatment interact with or counteract any other treatments I am taking?
- What new drugs are in development and when will they become available?
- Will taking this treatment affect whether I can take part in clinical trials in the future?
- How do I get the disease modifying drugs?
- Who will help with administration?

In situations where certain tests are involved, such as blood tests or cardiac monitoring, these questions may be helpful:

- What are the tests for?
- Will they cause a delay in starting my treatment?
- If they reveal another medical condition, will I still be able to take the disease modifying drugs?
- Will they hurt, or are there risks involved?
- Where do I have to go to have these tests?

4. Further sources of information and support

MS specialist nurse

An MS specialist nurse will talk through the prescription process, give practical advice and training, and offer patient support while adapting to treatment with the drugs and throughout the course of treatment. This usually takes place at a nurse-led disease modifying drug clinic. To locate an MS specialist nurse contact the MS Trust information service or see 'Map of MS Services' on the website www.mstrust.org.uk/map

MS Trust publications

Website

- **Disease modifying drug therapies – online**
  For up to date information on the current approved drug therapies www.mstrust.org.uk/dmts
- **Treatments in development**
  Provides information on drug therapies in clinical development www.mstrust.org.uk/did

Books

- MS Explained

Factsheet

- Clinically isolated syndrome (CIS)

MS Trust information service

The MS Trust information service is available to answer any questions about MS.

Contact by freephone: 0800 032 3839 (Monday to Friday 9am-5pm) or email infoteam@mstrust.org.uk

About the author

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The MS Trust is a UK charity for people with MS, their family and friends. The MS Trust information service offers a personalised enquiry service; produces a wide range of publications including Open Door, a quarterly newsletter; and provides web based information.

Thank you to

- All the people with MS who reviewed this book and made invaluable comments, including Tracy Nicholson of the MS Trust
- The following MS specialists for their help in preparing this publication: Trevor Pickersgill, Pauline Shaw, Karen Vernon, Alan Izat, Karen Little
- Representatives from the pharmaceutical manufacturers.

Please contact the MS Trust information team if you would like any further information about the reference sources used in the production of this publication.

This publication will be reviewed in three years.

The MS Trust online resource for disease modifying therapies is regularly updated. See www.mstrust.org.uk/dmts for the most up to date information.

Janice Sykes
Disease modifying drug therapy
2014 - 15 edition

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