Waldenström’s macroglobulinaemia and lymphoplasmacytic lymphoma

This page is about lymphoplasmacytic lymphoma, an uncommon type of non-Hodgkin lymphoma. Nearly all lymphoplasmacytic lymphomas are a type known as ‘Waldenström’s macroglobulinaemia’.

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What is lymphoplasmacytic lymphoma?

Lymphoma is a cancer of the lymphatic system, which is part of your immune system. It develops when lymphocytes (a type of white blood cell) become out of control. Lymphoplasmacytic lymphoma (LPL) is a rare type of non-Hodgkin lymphoma that develops from B lymphocytes (B cells). For more detail, you might also find our other information about lymphoma useful – what it is and what the different types of lymphoma are.

As part of a healthy immune system, some of the B cells turn into specialised cells called ‘plasma cells’. Their role is to produce proteins called ‘antibodies’. Antibodies help the immune system to recognise infections and substances that shouldn’t be in the body.

In LPL, B cells that are in the process of turning into plasma cells start to grow or divide in an abnormal way. They become cancerous lymphoma cells. In LPL, the lymphoma cells build up in the bone marrow (the spongy tissue in the centre of some of the large bones where blood cells are made), the spleen and the lymph nodes (glands).

When pathologists (doctors who study diseased tissues under a microscope) look at a sample of cells from a biopsy of LPL, they see a mixture of cancerous lymphocytes and plasma cells. This is why these types of lymphoma are described as ‘lymphoplasmacytic’.
The abnormal lymphoma cells that build up in large numbers in someone with LPL often produce large amounts of antibodies. However, the antibodies produced by these abnormal cells are not useful to your body the way normal antibodies are. These antibodies can even have harmful effects on the body if they target your body’s own tissues or organs. In the majority of cases, the associated antibody is IgM, and these cases are a type of LPL called ‘Waldenström’s macroglobulinaemia’.

LPL is a low-grade lymphoma, which means it usually develops slowly over a period of months or even years.

What types of LPL are there?

There are a few different types of LPL but nearly all LPLs are a type known as ‘Waldenström’s macroglobulinaemia’ (WM). It is named after Jan Waldenström, a Swedish doctor who first described the condition in 1948.
‘Macroglobulinaemia’ means that there is more of the macro (large) type of immunoglobulin (IgM) in the blood than is normal.

The chemical name for an antibody is ‘immunoglobulin’ (Ig for short). There are 5 types of immunoglobulins formed in the body: IgA, IgD, IgE, IgG and IgM. They each have a different function and are found in different areas of the body.

In WM, the lymphoma cells produce a type of antibody called ‘IgM’. This is the largest type of antibody and it is normally the first type of antibody you make in response to an infection. High levels of IgM can cause hyperviscosity (thickening of the blood) and some of the most common symptoms of WM.

Around 1 in 20 people with LPL don’t produce abnormal levels of immunoglobulin or produce another type of immunoglobulin, like IgG or IgA. In this case, the lymphoma is called ‘lymphoplasmacytic’ lymphoma, not WM. These other types of immunoglobulin are smaller and less likely to cause hyperviscosity. People who have no abnormal protein at all do not have problems with hyperviscosity.

Despite the fact that different antibodies are produced by the abnormal cells, all types of LPL are treated in the same way and the outcome is thought to be similar for all types of LPL. We refer to these lymphomas as ‘WM’ in the rest of this page.

Who gets Waldenström’s macroglobulinaemia and why?

WM is an uncommon type of lymphoma. Most people who develop WM are over 65. It is slightly more common in men than in women.

Scientists don’t know what causes WM. Autoimmune conditions like Sjögren syndrome might increase the risk of developing WM. Some research has shown that WM might be linked to hepatitis C infection or to other viral infections. However, not all studies have shown these links. Scientists do know that:
WM is not infectious – it cannot be picked up from, or passed on to, other people.

WM can occur in clusters within families – about 1 in 5 people with WM have a relative with either WM or a similar type of non-Hodgkin lymphoma, like chronic lymphocytic leukaemia (CLL).

Certain mutations (changes) in the genes are common in people with WM, especially mutations in a gene called ‘MYD88’, which occurs in nearly everyone with WM. Mutations in a gene called ‘CXCR4’ are also common and occur in around a third of people with WM. These are ‘somatic’ mutations, meaning they are not inherited from your parents; they are acquired in some of your cells after you are born. It is not known what causes these mutations. The role of these mutations in the behaviour and treatment of WM is a current focus of attention for researchers.

The risk of a family member developing lymphoma is still low, so there are no recommendations to check family members at present. If you are concerned, talk to your specialist for more information.

**Symptoms**

WM usually develops over many months or years. You might have no symptoms at all to start with. Some people with WM are diagnosed by chance, during a routine blood test or an investigation for another condition.

Most people with WM (and other types of LPL) have abnormal B cells and plasma cells in their bone marrow. The bone marrow is then not able to make as many normal blood cells as usual. This can cause:

- **anaemia** (shortage of red blood cells), leading to tiredness, weakness and breathlessness
- **neutropenia** (shortage of neutrophils, a type of white blood cell), leading to an increased risk of infections
- **thrombocytopenia** (shortage of platelets), leading to a tendency to bruise and bleed easily.
Many people have symptoms related to hyperviscosity because of high levels of abnormal immunoglobulins in their blood.

People with WM can also experience fevers, night sweats and weight loss, which are symptoms of many types of lymphoma. Doctors sometimes call these ‘B symptoms’.

Enlarged (swollen) lymph nodes are less common in people with WM than with other types of lymphoma. However, around 1 in 5 people with WM have swollen lymph nodes or a swollen spleen. A swollen spleen can cause discomfort or pain in your abdomen (tummy).

Rarely, lymphoma cells build up in other parts of the body and form masses or tumours. These are usually slow-growing and cause few symptoms. However, they can press on surrounding organs, nerves or blood vessels. This can cause pain or other symptoms in the affected area.

**What is hyperviscosity and what symptoms does it cause?**

If there is a large amount of IgM protein in the bloodstream in WM, it can cause hyperviscosity. This means your blood is thicker and flows more slowly than normal. It is sometimes called ‘hyperviscosity syndrome’ (HVS). Hyperviscosity can cause symptoms such as:

- nosebleeds
- blurring or loss of vision
- dizziness or headaches
- drowsiness, poor concentration or confusion
- shortness of breath because of heart failure or lung congestion.

Hyperviscosity can also cause changes to the back of your eyes (the retinas) because of pressure in your blood vessels. These changes can be seen using an ophthalmoscope, which is a handheld instrument available in GP surgeries and hospital clinics.
Figure: Blood vessels in a healthy eye
You might need **plasmapheresis** to relieve the symptoms of your hyperviscosity. This doesn’t stop hyperviscosity happening – you do need treatment for your WM as well.

The abnormal IgM in people with WM can cause **peripheral neuropathy** (nerve damage). This is common – about half of all people with WM develop peripheral neuropathy. You might have symptoms like weakness, tingling or numbness, usually in the fingers or toes. If you have peripheral neuropathy, you might have tests to look at your nervous system in more detail, like nerve conduction studies and scans.
In some people, IgM causes red blood cells to stick together in the cooler parts of the body such as your hands and feet, the tip of your nose or your ear lobes. You might have poor circulation in these areas, especially when it is cold. If you notice any colour changes or ulcers in these areas, tell your doctor. You might need to have a blood test to look for a protein called ‘cryoglobulin’.

If you have symptoms related to high IgM levels, you need to start treatment for WM to reduce your IgM levels.

Make sure you tell your doctor about all of your symptoms so that they can decide on the best treatment for you and when to start it.

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**Diagnosis**

WM is often suspected based on the results of **blood tests**, which can show anaemia or high erythrocyte sedimentation rate (ESR; a marker of inflammation). If WM is suspected, further blood tests are needed to:

- measure Ig levels
- confirm whether low blood counts (anaemia, neutropenia and thrombocytopenia) are associated with WM or another disorder
- look at your general health.

A **bone marrow biopsy** looks at the types and numbers of cells in your bone marrow.

A sample of your bone marrow might also be sent to a lab for genetic tests, although this is not routinely done at all centres. Nearly everyone with WM has been found to have a particular change in their genes. This is an MYD88 mutation and finding it can help confirm your diagnosis. About one-third of people with WM have another mutation in a gene called CXCR4. These mutations can affect how likely you are to respond to certain treatments. The results of genetic tests take 7–10 days to come back.

You might also have some or all of the following tests:
• An eye examination to look at the retina at the back of your eyes. The blood vessels in your retina can become enlarged or leaky because of the high levels of IgM protein in your bloodstream.

• Other biopsies, especially if you have swollen lymph nodes or a mass of lymphoma cells.

• Scans, such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound scans to assess whether your lymph nodes, liver, spleen or other places are affected by WM.

Your doctor should also ask about your symptoms and general health, and do a full physical examination.

Your Ig levels and scan results can be used as a baseline to see how you respond to treatment. If you have LPL and there is no abnormal Ig in your blood, bone marrow tests and scans are used to monitor your response.

Many types of lymphoma are ‘staged’, meaning the results of tests are used to determine how much of your body is affected by lymphoma. The staging system used in other lymphomas is not used for WM because the disease is often in the bone marrow rather than forming lumps.

Your doctor might mention a prognostic score. The International Prognostic Scoring System for WM (IPSSWM) is used to give your doctor an idea of how likely you are to respond to treatment. The score is calculated based on factors like your age and results of your blood tests. However, other factors like your general health are also important. Your doctor can give you more information about your prognosis (outlook) based on your individual circumstances.

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**Treatment**

WM is a slow-growing lymphoma that is normally treated to keep it under control, rather than to cure it. Most people live with this disease for many years. Your symptoms and test results are used to decide when to start treatment.

If you don’t have any symptoms, you might not need treatment straightaway. Instead, you have regular check-ups in the clinic. This active monitoring is
What is active monitoring (‘watch and wait’)?

WM develops slowly, sometimes with no symptoms at all to start with. You might not need any treatment for many years – about 6 in 10 people develop symptoms within 5 years of their WM being diagnosed. A few people never need treatment.

If your doctor decides that you don’t need treatment yet, you have regular check-ups, usually every 3–6 months. Your doctor asks how you are feeling each time. You also have blood tests to measure your blood cell counts and your IgM levels, if you have WM.

Many people with low-grade non-Hodgkin lymphoma, including WM, are on ‘watch and wait’. Research shows that it is better to save treatment until it is needed if your lymphoma is not causing you any problems. However, many people find it hard at first to know that they have lymphoma but are not having treatment. Talk to your medical team if you are worried. They can give you more information and support. You can also call our [helpline](#) – our team of dedicated patient support officers are trained to offer information on any aspect of lymphoma.

When does treatment start?

Treatment for WM usually starts if:

- you develop troublesome symptoms
- your blood IgM levels are increasing
- your blood cell counts change – you develop anaemia (low red blood cells), neutropenia (low white blood cells called neutrophils) or thrombocytopenia (low platelets).

What treatment will I have?

The first treatment for WM is usually a combination of the antibody therapy [rituximab](#) and [chemotherapy](#) drugs. [Steroids](#), such as dexamethasone, are
also commonly used. Several drugs that work in different ways are used to give the best chance of controlling abnormal cells. Regimens (combinations of drugs) that may be used include:

- DRC: rituximab with dexamethasone and cyclophosphamide
- BR: bendamustine with rituximab
- FR: fludarabine with rituximab
- FCR: fludarabine, cyclophosphamide and rituximab
- Clad-R: cladribine and rituximab.

Drug regimens are given in cycles over a period of a few months. In each cycle, you receive treatment some weeks but not others. The rest periods between treatments allow your body to recover before the next treatment. Your doctor should give you more information about the regimen they recommend, including information about the possible side effects.

Which regimen is chosen depends on individual factors, for example your general health and the symptoms you have. It also depends on what treatments you might need in the future. Certain drugs can reduce levels of stem cells (cells in your bone marrow that make blood cells). These drugs are best avoided if your doctor thinks you might need a stem cell transplant in the future.

Gentler chemotherapy drugs, like chlorambucil, might be used if you are not well enough for stronger chemotherapy. These drugs can be very effective.

If you have high IgM levels (30-40 g/L or higher), rituximab can temporarily cause IgM levels to increase further – this is sometimes called 'IgM flare'. It is not known why this happens in some people. However, the rise in IgM can lead to hyperviscosity which sometimes needs plasma exchange. Your IgM levels are monitored carefully during your treatment so that a response, when needed, can be quick.

If your doctor thinks you are likely to experience IgM flare, they might give you chemotherapy without rituximab for the first few cycles to reduce IgM. Rituximab can then be given for later cycles and after chemotherapy has finished.
Other chemotherapy regimens and other treatments may also be used – your medical team should discuss these with you if they are relevant to you. **Newer, targeted drugs** are being tested for WM and you may be offered a targeted drug for WM as part of a clinical trial.

### Research and targeted treatments

Newer, targeted drugs are being developed to treat many types of lymphoma, including WM. These usually target the abnormal cells more precisely, reducing the effects on normal cells. They might be given alone, in combination with other targeted drugs or in combination with chemotherapy. Drugs that are being tested in WM or similar types of low-grade NHL include:

- **drugs that block signals or the function of control proteins within the lymphoma cells**, which, depending how they work, can be grouped as:
  - **cell signal blockers**, eg ibrutinib (Imbruvica®), idelalisib (Zydelig®), everolimus (Afinitor®), perifosine and venetoclax
  - **proteasome inhibitors**, eg bortezomib (Velcade®), carfilzomib (Kyprolis®) and ixazomib (Ninlaro®)
- **newer antibodies against CD20**, the protein targeted by rituximab, eg ofatumumab (Arzerra®) and obinutuzumab (Gazyva®)
- **antibodies against targets on plasma cells**, eg daratumumab (Darzalex®).

Another area where there is growing research in lymphomas and other cancers is **CAR T-cell therapy**. This involves engineering your own immune cells to recognise and attack your lymphoma cells. This is an area where there is a lot of interest, but trials are still in early stages.

At the time of writing, only **ibrutinib** is approved for use in people with WM.

The list above only includes drugs in later stages of testing. There are other drugs in early stage clinical trials and new drugs are being developed and tested all the time. Your doctor might recommend that you are treated with a targeted drug as part of a clinical trial. You can **find out more about clinical**
Treatments for symptoms and side effects

You might need other treatment for thickening of your blood, if your blood counts are lower than normal, or if you have side effects from your chemotherapy drugs. This is sometimes called ‘supportive care’ as these treatments don’t treat the lymphoma but support your body through your lymphoma treatment.

You might be given:

- antibiotics to prevent infections that can occur because of low blood counts during treatment, eg if you have neutropenia (low neutrophils)
- anti-viral drugs – some viruses that remain dormant in your body can be reactivated when you are treated for lymphoma
- **blood transfusions**
- immunoglobulin replacement therapy
- plasmapheresis

**Blood transfusions**

Your WM can cause **anaemia** (low red blood cell count) or **thrombocytopenia** (low platelet count). Chemotherapy also affects your bone marrow and can cause low blood cell counts. If your blood cell counts are too low and you develop troublesome symptoms, your medical team might give you a **blood transfusion**. You might have a platelet transfusion, which is given in the same way.

If you have **hyperviscosity**, you might need **plasmapheresis** to thin your blood before a blood transfusion. This is needed to prevent your blood becoming even thicker because of the transfused red blood cells.
Immunoglobulin replacement therapy

Some people with WM do not make enough normal antibodies to fight infection. This can put them at a higher risk of developing serious infections. If this is the case for you, you might be offered **immunoglobulin replacement therapy**. This is an infusion of antibodies to help boost your antibody levels.

Plasmapheresis (plasma exchange)

If you have too much **IgM protein** in your blood, you might develop **hyperviscosity**. Should this happen, you might need to have your blood thinned by a procedure called ‘plasmapheresis’ (plasma exchange).

In this procedure, a cannula (soft tube) is placed into a vein in each of your arms. Blood is slowly removed from one arm. It is then passed through a machine that separates the liquid part of the blood, the plasma (which contains the IgM protein), from the blood cells. The blood cells are then combined with an artificial plasma substitute and returned into your other arm.

The whole process takes about 2 hours. You might only need to have plasmapheresis once, before your treatment for WM reduces your IgM levels. However, you might need to have this procedure several times depending on your symptoms and how quickly your WM treatment works.

More information on plasma exchange is available from **NHS Choices**. Your hospital should give you detailed information if you need this procedure.

Relapse

Although treatment is likely to put your WM into remission (no evidence of the disease), WM usually **relapses (comes back)**. You might not need treatment straightaway. Your doctor may decide to ‘watch and wait’ again, until treatment is needed. Should you need treatment, you might be treated with the same regimen you had before or a different one. Your doctor decides what treatment is best for you based on a number of factors:

- how you coped with the treatment you had before
• how long it has been since you finished your last course of treatment
• your general health.

The same treatment can often be used again if you have been in remission for 2 years or more. If your WM relapses sooner, you might be given a different drug or combination of drugs. Some people might be able to have ibrutinib or another targeted drug through a clinical trial. Your doctor might recommend a stem cell transplant.

A stem cell transplant is an intensive form of therapy. It is only considered if you are well enough to have it. If you have relapsed lymphoma, you have to respond to chemotherapy and be in remission (no evidence of lymphoma) again to be able to have a stem cell transplant in the UK.

The stem cell transplant is given after high-dose chemotherapy to help to make the remission last longer. Most stem cell transplants in people with WM are autologous (using your own cells) rather than allogeneic (using donor cells) stem cell transplants.

Transformation

In up to 1 in 10 people, WM turns into a faster growing (high-grade) type of lymphoma, usually diffuse large B-cell lymphoma (DLBCL). This process is called ‘transformation’. If it happens, you might get new symptoms like swollen lymph nodes or a mass that grows quickly.

You have a biopsy of the swollen lymph node or mass and other tests, like scans. The results of your tests tell your medical team if your WM has transformed and whether the transformed lymphoma is in 1 place or several places.

If your lymphoma transforms to become faster growing, you need a different type of treatment. Transformed WM is treated like a high-grade lymphoma. Most people have chemotherapy with rituximab. Some people have intensive chemotherapy and a stem cell transplant.
Follow-up

WM is a low-grade lymphoma that you can have for many years. It is very likely to relapse at some point after treatment. You need to be followed up regularly in the outpatient department, usually every 3–6 months.

As part of your check-ups, you have regular blood tests to check the level of the IgM protein and your blood counts.

Tell your doctor if you develop symptoms, including any that have come back since your last treatment, new symptoms or worsening of existing symptoms. If you develop any new or worsening symptoms between appointments, contact your medical team. They can bring your next appointment forward if they think they need to see you sooner.

Depending on your blood test results and symptoms, you might have another bone marrow biopsy or CT scan to reassess your condition at your follow-up appointment. If you have a type of LPL that doesn’t produce high levels of protein, bone marrow biopsies and CT scans are used to assess how well the treatment has worked.

Your doctor will recommend that you have certain vaccinations, like an annual flu vaccination and vaccination against Streptococcus pneumoniae and Haemophilus influenzae type B (HiB). However, vaccinations should be avoided 2 weeks before, during and for 6 months after chemo-immunotherapy. You should not have live vaccines, for example for polio, shingles or yellow fever.

Living with WM

Most people live with WM for many years. You might find the information about living with lymphoma helpful. It covers the everyday aspects of living with a chronic (long-term) condition, such as coping with tiredness, the effect of the diagnosis on your feelings and relationships, plus financial matters, travel and vaccinations.

The following organisations offer further information and support specifically to people affected by WM.
- **WMUK** - a UK point of contact for people with WM. WMUK has a support group and helpline and runs an annual WM seminar.

- **International Waldenström’s Macroglobulinemia Foundation (IWMF)** - An international charity based in the United States that provides information and support for people with Waldenström’s macroglobulinaemia.

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**References**

These are some of the sources we used to prepare this information. The full list of sources is available on request. Please contact us by email publications@lymphoma-action.org.uk or phone on 01296 619409 if you would like a copy.


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**Further reading**

- Living with lymphoma
Glossary

Chemotherapy

Ibrutinib

Active monitoring (‘watch and wait’)

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