

Introduction

Behçet's *syndrome* (or Behçet's *disease*) is a multisystem disorder, in which potentially any organ can be affected, and also because so little is known about the cause of this condition, treatment of Behçet's is a considerable challenge. As a cure is currently not possible, the strategy for treating Behçet's today is therefore to suppress disease activity as much as possible without the patient paying the price of unacceptable side effects. This means the doctor choosing from a wide variety of drugs available, to tailor therapy at the right time to the right person. This is likely to vary from patient to patient:

Some patients may only need therapy when they suffer from a flare-up – for much of the time, they may not require any drug treatment at all.

Other patients, with more severe and persistent disease, will need chronic (long term) therapy to suppress disease and minimise the occurrence of flares.

When a major organ, such as the eye, is threatened by critical involvement, there is an urgent need for often the most powerful drugs, to minimise damage.

Perhaps one of the most important principles in caring for Behçet's is that patients are managed by a specialist with expertise in this rare disease. While rheumatologists, ophthalmologists and dermatologists are the specialists most likely to encounter patients with Behçet's, some will have more experience and knowledge of this condition than others. The fact that many different organs can be involved means that often a team of different specialists is needed. In this case, it is important for one of them to take the lead and coordinate the care.

Treatment of specific complications

Mouth and genital ulcers

Mouth and genital ulcers are extremely common and can range in severity from a nuisance to an extremely painful and disabling problem. Steroids can help considerably, but care should be taken if they are needed in large amounts and for prolonged periods, as they may cause unacceptable side effects and toxicity.

- Topical steroids, where medication is applied directly to the ulcers, are the first line of treatment.
- Many patients find that squirting steroid sprays, normally used to treat asthma, directly onto an ulcer, will deliver a high dose directly to the right place – without side effects.
- Steroid mouthwashes (with or without antibiotics or an antifungal agent) or sometimes lozenges are often helpful.
- Steroid creams can be applied directly to genital ulcers.
- Regular low-dose colchicine may be effective in reducing the number and severity of flare-ups with ulcers.

Joint pain

Sore and aching joints (arthralgia) are a very common problem.

- Simple painkillers such as paracetamol and co-codamol may help.
- Many patients may benefit from a non-steroidal anti-inflammatory drug (NSAID) such as diclofenac, naproxen or a coxib such as celecoxib or etoricoxib.
- Occasionally, musculoskeletal pains may require an opiate, but this should be resisted where possible and other therapies such as immunosuppression considered.

Eye disease

The development of eye inflammation in Behçet's is a source of concern and must be taken extremely seriously, with full assessment by an experienced ophthalmologist – especially if the eyes look red and the vision is blurred. A range of treatments may be required, depending on the pathology, (the cause of the inflammation and how serious it is) including:

- Steroid eye drops.
- Direct injection of steroid.
- Oral or intravenous steroids and/or immunosuppressive agents (e.g. cyclophosphamide – see below).
- A TNF inhibitor such as infliximab – see below.
- Interferon-alpha (see below).
- Laser treatment.

Headaches

Headaches are frequently reported in Behçet's and can sometimes be difficult to relieve.

- Typically, the headaches in Behçet's should be managed as 'normal' migrainous headaches, with prevention by beta-blockers such as propranolol or triptans such as sumatriptan (often in combination with an NSAID). An antidepressant may also help.
- Occasionally, headaches in Behçet's reflect serious intracranial involvement with raised intracranial pressure and venous sinus thrombosis. This means a disturbance of blood drainage from the brain leading to an increased pressure in the brain.
- The onset of a new headache, especially with neurological involvement, requires urgent assessment with neurological examination, fundoscopy (a test used to see inside the furthest point at the back of the eye, the fundus, using an ophthalmoscope) and often MRI scanning of the head.

Skin rashes

Behçet's causes many different types of skin rash. It is important to get the correct diagnosis for the rash, as this may affect the choice of treatment. Many localised skin rashes respond to topical steroid creams and sometimes colchicine. A generalised rash is likely to require systemic therapy. This means taking medicine by mouth (as tablets), or as injections/infusions, rather than being applied to the affected area. Typically, this will involve combinations of steroids and other immunosuppressants, which work by suppressing the overactive immune system.

Thromboses

There is an association between a subset of patients with Behçet's and the development of thrombosis, or blood clots within the veins.

- An episode of deep vein thrombosis (DVT) should be managed as usual, with heparin initially followed by conversion to warfarin. Further episodes may require chronic warfarin therapy.
- The possibility of active disease in other organs should be considered in DVT and managed accordingly.

Treatment of more widespread disease that is not responding to first-line treatment

Many patients with Behçet's have disease that is severe and do not respond to the first-line drugs listed above. In these situations, systemically active immunosuppressants or cytotoxic drugs are used – given by mouth, intramuscularly or by intravenous drip. These drugs must be given under expert specialist supervision and need regular monitoring to detect potential side effects and determine response.

A wide variety of drugs are available, but as yet it is not possible to predict which patient will respond to what drug. It is therefore useful to swap drugs after a suitable trial if they are ineffective. Drugs often used in these situations include:

- Azathioprine (requiring monitoring for bone marrow and liver side effects).

- Care must be taken to allow up to three months for azathioprine to be effective.
- Dapsone (with potential side effects of haemolytic anaemia and liver toxicity).
- Chlorambucil (with monitoring for possible bone marrow toxicity).
- Tacrolimus, cyclosporine and mycophenolate mofetil (with potential for renal side effects and development of high blood pressure).

Cyclophosphamide is a cytotoxic drug (a drug that destroys or damages particular cells), developed for the treatment of cancers and leukaemia. In Behçet’s disease, it is used mainly in:

- Severe eye disease.
- Inflammation within the brain.
- Systemic (or organ-threatening) vasculitis.

Thalidomide has been used with some success in the management of refractory mucocutaneous Behçet’s (which means the management of oral and genital ulcers which have not responded to the first lines of treatment). This drug can only be prescribed by a specialist registered for this purpose. Its use is quite limited, as it must never be used when there is any chance of potential pregnancy and, as well as the well-known risk of inducing birth defects, it carries a high chance of inducing peripheral neuropathy. (This means damage to the network of nerves which carry messages to the brain and the spinal cord from the rest of the body.)

More recent therapies

Biologic agents (protein-based drugs designed to specifically inhibit components of the inflammatory pathways), originally developed to treat other inflammatory conditions such as rheumatoid arthritis, are proving most useful in managing severe Behçet’s. As these drugs are proteins, they cannot be taken orally and must be given by injection (either under the skin or intravenously). They are also extremely expensive and are therefore reserved for severe disease, when other powerful drugs have failed.

- Interferon-alpha is proving to be a drug particularly helpful with eye involvement and potentially other organs in Behçet’s.
- Tumour necrosis factor alpha (TNF) inhibitors – such as infliximab, adalimumab and etanercept – have proven especially useful in severe Behçet’s. As with all immunosuppressant agents, they increase susceptibility to infection.
- Alemtuzumab (Campath) is normally used for leukaemias and multiple sclerosis. This is not a drug to be taken lightly and should only be used in experienced departments. It often causes severe infusion reactions and can weaken the immune system significantly, but it has been found to be effective in many patients with Behçet’s when other drugs have failed.

Bone marrow transplantation is only very rarely needed. It is a very serious procedure but has resulted in good outcomes for patients with the most severe forms of disease.

Summary

A wide variety of drugs may be used in Behçet’s. The choice of drug must be tailored to the patient and his or her disease. It is essential that such treatment is led by a specialist with expertise not only in Behçet’s but also in the delivery of such medications. The best care is provided by a team of specialists working together, each able to bring his or her particular expertise to the patient. In England, this occurs in the three national Behçet’s Syndrome Centres of Excellence (in Liverpool, Birmingham and London). In other devolved UK countries, whilst the Centres in England can be accessed, this will require prior approval (and funding) from local Health Boards.

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