Behçet's Factsheet 4
Treatment

Introduction

Behçet's syndrome (or Behçet's disease) but more simply Behçet's, is a multisystem disorder, in which potentially any organ can be affected. 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 working with the patient to choose 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 and for much of the time may not require any drug treatment at all.

Other patients, with more severe and persistent disease, may need long term therapy to suppress their 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 choosing the most powerful drugs from the start, to suppress inflammation and 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, oral medicine physicians 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 in the same patient 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 - this is most often, but not always, a rheumatologist.

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 or ointments 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.
- Very severe ulcers that are resistant to treatment sometime require a more general approach, with drugs such as azathioprine, or biologics such as infliximab or adalimumab

Joint pain

Sore and aching joints (arthralgia) are a very common problem. Arthritis (causing swelling and damage to joints) is very unusual.

- Simple painkillers such as paracetamol and co-codamol may often 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.
- Very occasionally, musculoskeletal pains may require an opiate, but this should be resisted where possible because other therapies such as immunosuppression, or different ways to help pain (such as gabapentin/pregabalin or amitriptyline) may be better in these situations.
- Severe joint involvement with swelling and inflammation in a joint can respond to injection of steroid, oral azathioprine, but may often benefit from biologic treatment.

Eye disease

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

- Steroid eye drops.
- Direct injection of a long-acting steroid.
- Oral or intravenous steroids and/or immunosuppressive agents (see below).
- A biologic TNF inhibitor such as infliximab or adalimumab – 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 in the same way 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, such as weakness or strange sensations, requires urgent assessment with neurological examination, fundoscopy (a test used to examine the back of the eye, using an ophthalmoscope or slit lamp) and often MRI scanning of the head.

Skin problems or rashes

Behçet's causes many different types of skin problem. It is important to get the correct diagnosis for the rash, as this may affect the choice of treatment. Many localised rashes respond to topical steroid creams and sometimes colchicine. A generalised rash is more 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

A small group of patients with Behçet's are prone to the development of thrombosis, or blood clots within the veins. Arteries may also be involved. This is very serious and needs urgent attention.

- An episode of deep vein thrombosis (DVT) in Behçet's may not respond to the usual acute medical approach of blood thinners such as heparin, followed by later conversion to warfarin. If a patient with Behçet's has a DVT or pulmonary embolus (blood clot in the lungs) it may be due to sticky blood vessels, rather than the more usual sticky blood – and therefore may be best treated by steroids or other immunosuppressants such as infliximab, rather than the blood thinners that are used normally. Discussion and advice with the specialist in charge of the Behçet's is advised.
- 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 does not respond to the first-line drugs listed above. In these situations, systemically active immunosuppressant's or, rarely, cytotoxic drugs are used. These are given by mouth, by injection, or intravenous drip. These drugs must be given under expert specialist supervision and need regular monitoring to detect and minimise potential side effects and assess 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 often useful to swap drugs after a suitable trial if they are ineffective or not tolerated. 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).
- Tacrolimus, cyclosporine and mycophenolate mofetil (used carefully: as there is the potential for renal side effects, development of high blood pressure or sticky blood vessels).

Cyclophosphamide is a cytotoxic drug (a drug that destroys or damages particular cells), developed for the treatment of cancers and leukaemia. It is only very rarely used in Behçet's today, mainly for:

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

Thalidomide has been used with some success in the past for the management of refractory mucocutaneous disease (especially for 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 extremely limited as it is associated with many potential side-effects. It must never be used when there is any chance of pregnancy and, as well as the well-known association with birth defects, it carries a high chance of inducing peripheral neuropathy (damage to the network of nerves which carry messages to the brain and the spinal cord from the rest of the body) and unacceptable fatigue

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 expensive and are therefore reserved for severe disease, when other powerful drugs have failed.

- 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.
- Rituximab, used for blood disorders and some forms of arthritis and vasculitis, can be effective in some patients with Behçet's, especially with some forms of eye disease
- 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 very experienced departments and in limited situations. It often causes severe infusion reactions and can weaken the immune system significantly for long periods, but it has been found to be effective in some patients with Behçet's when other drugs have failed.
- Other biologics such as secukinumab, ustekinumab or tocilizumab are currently being evaluated for use in Behçet's.

Bone marrow transplantation is used here only exceptionally rarely. It is a most 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 their 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 their particular expertise to the patient. In England, this occurs in the three national Behçet's Syndrome Centres of Excellence (in Liverpool, Birmingham and London). The devolved UK countries can also access the Centres in England can be accessed, but require prior approval (and funding) from their local Health Boards before their patients can be seen.

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