Treatment of Behçet’s Disease (BD)

Introduction

Because Behçet’s Disease is a multisystem disease, where potentially any organ can be affected, and also that so little is known about the cause of this condition, treatment of Behçet’s disease is a considerable challenge. As cure is currently not possible, the strategy for treating BD today is therefore to suppress disease activity as much as possible without the patients paying the price of unacceptable side-effects. This means the doctor choosing from a wide armamentarium of drugs, to tailor therapy at the right time to the right person. This is likely to vary from patient to patient:

- Some patients may only require 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 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 BD is that patients are managed by a specialist with expertise in this rare disease.

- Whilst rheumatologists, ophthalmologists and dermatologists are the specialists most likely to encounter patients with BD, some will have more experience and knowledge of this condition than others
- The fact that many different organs can be involved in BD means that often a team of different specialists are needed. In this case, it is important for one of them to take the lead and co-ordinate the care

Mouth and Genital Ulcers

Mucocutaneous ulcers are extremely common and can range in severity from a nuisance to a nasty painful and disabling problem. Steroids can help considerably, but this must not be allowed to be at the expense of toxicity.

- Topical steroids are the first line of treatment.
- Many patients find that squirting steroid sprays, normally used to treat asthma, directly on to an ulcer will deliver a high dose directly to the right place – without systemic side effects
- Steroid mouthwashes (with or without antibiotics) 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 Pains

Sore and aching joints (arthralgia) is a very common problem.
• Simple analgesics such as paracetamol and co-codamol may help
• Many patients benefit from a non-steroidal anti-inflammatory (NSAID) drug such as diclofenac, naproxen or a coxib such as celecoxib or etoricoxib.
• Occasionally musculoskeletal pains may require a synthetic or conventional opiate – but this should be resisted where possible and other therapies such as immunosuppression considered.

Eye Disease
The development of eye involvement in BD 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, including:
• Steroid eye drops
• Direct injection of steroid
• Oral or intravenous steroids and/or immunosuppressive agents (e.g. cyclophosphamide – see below)
• Interferon alpha (see below)
• Laser treatment

Headaches
Headaches are particularly common in BD and can be sometimes difficult to relieve.
• Typically, the headaches in BD should be managed as for “normal” migrainous headaches with preventatives by beta blockers such as propranolol or triptans such as sumatriptan (often in combination with an NSAID). An antidepressant may also help (see section on headaches)
• Occasionally, headaches in BD reflect serious intracranial involvement with raised intracranial pressure and venous sinus thrombosis (see section on neurological involvement).
• The onset of a new headache, especially with neurological involvement requires urgent assessment with neurological examination, fundoscopy and often MRI scanning of the head.

Skin Rashes
Behçet’s Disease 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, which may involve combinations of steroids and other immunosuppressants.

Thromboses
There is an association between a subset of patients with BD and the development of thrombosis, or blood clots within the veins.
• An episode of deep vein thrombosis (DVT) should be managed as normal, with heparin initially, then converted 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 refractory disease

Many patients with BD 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 trial of a month or so, if they ineffective. Drugs often used in these situations include:

- Azathioprine (requiring monitoring for bone marrow and liver side-effects)
- Dapsone (with potential side effects of haemolytic anaemia and liver toxicity)
- Chlorambucil (monitored for possible bone marrow toxicity)
- Tacrolimus, cyclosporin and mycophenolate mofetil (with potential for renal side-effects and development of high blood pressure)

Cyclophosphamide is a cytotoxic drug developed for the treatment of cancers and leukaemia. In BD, 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 BD in many patients.

- 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.

More recent therapies

Biologic agents (protein-based drugs designed to specifically inhibit components of the inflammatory pathways) have recently been developed to treat other inflammatory conditions such as rheumatoid arthritis. They are also proving most useful in BD. 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 specialists must make a special case to the bodies that fund drug treatment (Primary Care Trusts in the UK) for permission to use them. They are therefore reserved for the most severe disease when other powerful drugs have failed.

- Interferon alpha shows promise as a drug that may particularly help with eye involvement and ulcers. A clinical trial is currently underway in the UK to determine its true value in BD
- Tumour necrosis factor alpha (TNFα) inhibitors infliximab, adalimumab, and etanercept have all proven particularly useful in BD. As with all immunosuppressant agents, they increase susceptibility to infection

Summary

A wide variety of drugs may be used in BD. 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 BD, but also in the delivery of such medications – and often, the best care is provided by a team of specialists who are each able to bring their particular expertise with the patient at the centre.

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