Oxford University Hospitals NHS
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Clinical Commissioning Group

Dapsone for the treatment of dermatitis herpetiformis and other dermatoses

Shared Care Protocol

This protocol provides prescribing and monitoring guidance for Dapsone therapy for the treatment of dermatitis and other dermatoses. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Shared Care Responsibilities

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Specialists must contact GPs as soon as decision is made to commence treatment with Dapsone to ensure adequate time for full communication, support and agreement to be made. **Specialists must retain prescribing until the patient's clinical condition is stable or predictable.**

Specialist

- Complete pre-treatment assessment (detailed below) including necessary pre-treatment testing
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria and include this protocol
- Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Provide contact details to patient (including out of hours).
- Provide copy of patient information leaflet and drug monitoring card where appropriate
- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care *(The expectation would be for the specialist to prescribe a minimum of the first 28 days of treatment)*
- Ensure patient agrees before requesting or commencing shared care.
- Ensure discharge/outpatient letter on commencement of shared care includes all initial monitoring results and patient preferences
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient throughout treatment

GP

- Accept shared care or contact specialist to discuss concerns/any additional support required. Unless any concerns are raised by the GP within 14 days, shared care will be assumed and the patient will collect the next prescription from the GP
- Provide contact details to patient (including out of hours).
- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to the specific shared care protocol (listed under on-going monitoring).

- Check and record results then advise the specialist of any deteriorations or abnormal results
- Notify the specialist to any changes in patients condition, any adverse drug reactions or failure to attend tests

Patient

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Attend for blood tests and monitoring when required
- Ensure monitoring card is kept up to date and is brought to all appointments
- Report any side effects to the GP or a member of the specialist team

Background for Use

Dapsone is an antibacterial and antiprotozoal agent belonging to the sulfonamide class of antibiotics. It additionally acts as an anti-inflammatory drug and has successfully been used to treat a range of inflammatory skin diseases. Dapsone is licensed for use in dermatitis herpetiformis but is also used for a range of other unlicensed indications including other autoimmune blistering diseases (linear IgA disease, pemphigus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita), subcorneal pustular dermatosis, cutaneous vasculitis, lupus erythematosus, pyoderma gangrenosum, hidradenitis suppurativa, severe acneiform eruptions, erythema elevatum diutinum, granuloma faciale and Sweet syndrome.

This shared care protocol covers the use of dapsone to treat dermatitis herpetiformis and other dermatoses in adults. Dapsone is licensed as a treatment for a number of other indications outside dermatology but these are outside the scope of this shared care protocol.

Supporting Information

Dermatitis herpetiformis:

Dapsone is first line systemic treatment for patients with dermatitis herpetiformis. A few case series have been published demonstrating its efficacy in dermatitis herpetiformis but randomised controlled trials are lacking.[1-4]

Other autoimmune blistering diseases:

One very small randomised, double-blind, placebo-controlled trial evaluated the use of dapsone as a glucocorticoid-sparing agent in the maintenance phase of treating pemphigus vulgaris. Overall, 8 of 11 patients (73%) receiving dapsone versus 3 of 10 (30%) receiving placebo reached the primary outcome measure of requiring 7.5mg/day or less of prednisolone.[5] A retrospective review of case reports and series evaluating dapsone for pemphigus found that 96% patients responded to dapsone alone or in addition to other systemic immunosuppressants.[6]

There are no randomised controlled studies evaluating dapsone in the treatment of bullous pemphigoid but there are published studies describing its use for this indication.[6,7,8] Of these patients, 82% showed clinical improvement with 50-300mg/day of dapsone alone or in combination with other immunosuppressants.

A randomized double-blind non-placebo controlled trial comparing cyclophosphamide and dapsone for the treatment of mucous membrane pemphigoid found cyclophosphamide to be superior.[9] It has been suggested that mucous membrane pemphigoid of mild-moderate severity responds to dapsone and may therefore be a better first line option given its safer side effect profile compared to cyclophosphamide.[10]

Retrospective analysis of reports of dapsone treatment in patients with epidermolysis bullosa acquisita found this to be an effective treatment in combination with prednisolone.[11]

Dapsone is considered to be the first-line therapy for linear IgA disease (linear IgA bullous dermatosis).[12] A retrospective study evaluating dapsone in children with linear IgA disease also found this to be an effective treatment.[13]

Other inflammatory dermatoses:
Dapsone is first-line therapy for subcorneal pustular dermatosis (Sneddon-Wilkinson syndrome).[14] It is also an established treatment option for the management of cutaneous small vessel vasculitis.[15] Dapsone can be used as an adjunctive treatment in cutaneous lupus erythematosus.[16] Case reports and series have reported the efficacy of dapsone in treating pyoderma gangrenosum, often in conjunction with an immunosuppressant agent, and a recent retrospective case review indicated that dapsone could be an effective and tolerable non-immunosuppressant treatment for this condition.[17] The 2018 British Association of Dermatologists guidelines for the management of hidradenitis suppurativa recommend that dapsone is considered as a treatment option in patients who are unresponsive to antibiotic therapies.[18] The rare neutrophilic dermatoses erythema elevatum diutinum and granuloma faciale are both responsive to dapsone, making it an appropriate treatment option for these conditions.[19,20] Although Sweet syndrome (acute febrile neutrophilic dermatosis) is typically managed with topical and/or systemic corticosteroids, dapsone is an effective second-line treatment option.[21]

Contraindications and Precautions

Contraindication	**Action**
Known hypersensitivity to sulphonamides, sulphones or any of the excipients	Do not prescribe dapsone
Severe / symptomatic anaemia	Do not prescribe dapsone
Porphyria	Do not prescribe dapsone
Severe G6PD deficiency	Do not prescribe dapsone
Hereditary problems of galactose intolerance, the LAPP lactose deficiency, or glucose-galactose malabsorption	Do not prescribe dapsone

Precautions	**Action**
Co-existent cardiac, pulmonary, cerebrovascular or peripheral vascular disease	Use dapsone with caution; initiate at lower dose than normal (e.g. 25mg/day)

Anaemia	Severe anaemia should be treated before starting dapsone
Methaemoglobin reductase deficiency or Haemoglobin M	Use dapsone with caution; initiate at lower dose than normal (e.g. 25mg/day)
Pregnancy	Dapsone has been used safely in pregnancy but neonatal haemolysis and methaemoglobinaemia has been reported in the third trimester. If dapsone is necessary, folic acid supplementation (5mg/day) should be prescribed to the mother prior to conception and throughout pregnancy.
Breast feeding	Dapsone is present in breast milk and a case of haemolytic anaemia in a breastfed infant has been reported. Risks to the infant are thought to be very small unless the infant is G6PD deficient. Seek specialist advice.

Dosage

Indication	Dose
Dermatitis herpetiformis and other dermatoses	The typical starting dose is 50mg once daily, increased by 50mg/day at 2-4 weekly intervals, if required, to a maximum dose of 300mg/day. Once the condition is controlled, the dose should be reduced to the lowest dose required for maintenance which may be continued longer term for a number of years. In elderly patients, a smaller starting dose of 25mg once daily may be used. The paediatric dose is 1-2mg/kg/day with a maximum dose of 100g daily. Adolescent patients are prescribed 50-100mg daily.

Time to Response

Most patients with dermatitis herpetiformis will respond to dapsone within 24-36 hours of initiating the medication and withdrawal of dapsone results in recurrence of signs and symptoms within 24-48 hours.
The response of other inflammatory dermatoses to dapsone is typically slower than for dermatitis herpetiformis, occurring within weeks to three months.

Pre-Treatment Assessment

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Full blood count (FBC) including differential white cell count and mean cell volume
- Reticulocyte count
- Urea, electrolytes and creatinine (U+E)
- Liver function tests (LFT) – bilirubin, ALT and ALP

Ongoing Monitoring

- FBC
- Reticulocyte count – this is not reported in standard FBC results and must be specifically requested
- U+E
- LFT - bilirubin, ALT and ALP

The above tests should be performed weekly for the first month of treatment, then monthly for the next three months, then once every three months.

Following dose increases, they should be performed more frequently (e.g. weekly for one month, then monthly for three months, then every three months).

Clinical monitoring

The patient would typically be reviewed in the dermatology clinic at least every six months once stable on treatment, or potentially every twelve months if on a very stable dose of dapsone for a long period of time (e.g. >18 months). Patients would be reviewed more frequently e.g. every 3 months earlier on during the course of their treatment to assess their response and adjust the dosing as required.

The decision as to whether to stop or alter the dose of dapsone would be the responsibility of the prescribing dermatologist and would be discussed in detail with the patient first in clinic. The patient's GP would not be expected to make this decision at the time of the patient's regular medication reviews.

Adverse effects of dapsone

Common:
Stomach upset (take dapsone with food or milk if this occurs); anorexia; nausea; vomiting; headache; lethargy; mild haemolysis; methaemoglobinaemia; sulphaemoglobinaemia

Infrequent:
Depression; rash; moderate/severe haemolysis; hepatitis; motor/sensory neuropathy

Rare:
Agranulocytosis; hypoalbuminaemia; insomnia; psychosis; nephrotic syndrome; reduced fertility

Serious adverse effects (see table below for actions to be taken):

- Dapsone hypersensitivity syndrome

  Presentation includes pruritus, dermatitis, lymphadenopathy and fever. Arises in 1/100 patients, typically within 6 weeks after starting dapsone. A peripheral eosinophilia may be present. If these symptoms occur, dapsone should be stopped immediately and the hospital specialist should be contacted.

- Haemolytic anaemia

  Haemolysis can occur between 2 days – 4 weeks after starting dapsone. Some degree of haemolysis is inevitable. Provided the patient remains well and haemoglobin levels stabilise, this is not an indication to stop dapsone.

- Methaemoglobinaemia

This is a common side effect of dapsone and can be significant for patients with cardiopulmonary disease. Provided the patient remains well and levels stabilise, it is not an indication to stop dapsone. It peaks at about two weeks after starting treatment. If the patient develops symptoms including light headedness, shortness of breath or fatigue, serum methaemoglobin levels should be measured. In general, >15% methaemoglobin is associated with central cyanosis; >30% is associated with shortness of breath, light headedness and headache and >60% is associated with coma.

- Agranulocytosis

This is rare and usually occurs within 3 months of starting treatment. If the patient develops fever, sore throat, mouth ulcers, easy bruising or other symptoms suggesting infection, FBC should be checked immediately. If abnormal, dapsone should be stopped and the hospital specialist contacted.

- Neuropathy

Peripheral neuropathy (usually motor) can develop with prolonged use of dapsone but is rare if doses <300mg/day.

- Hepatitis

- Renal papillary necrosis and nephrotic syndrome

Actions to be taken

Please note, some degree of haemolysis is expected with the use of Dapsone. It occurs within the first month, stabilises and improves. Provided the patient remains well and levels stabilize, this is NOT an indication to stop dapsone. If the patient's MCV falls, consider the need for iron supplementation.

Blood test result	**Action**
>2 fold rise in alanine transaminase (ALT) above the upper limit of reference range	Check for other causes of elevated LFT including alcohol excess / infection / other medications. If persistently elevated without other obvious case, suggest stopping dapsone and contact hospital specialist.
>4 fold rise in ALT above the upper limit of reference range	**Stop dapsone** and immediately discuss with hospital specialist
White cell count <2.5 x 10*9/L Neutrophils <2.5 x 10*9/L Haemoglobin fall of >20g/L from baseline	**Stop dapsone** and immediately discuss with hospital specialist
Platelets <150 x 10*9/L	Consider other causes; discuss with hospital specialist
Reticulocyte count	If there is a steady rise in reticulocyte count accompanied by a decrease in haemoglobin and/or signs or symptoms of anaemia, discuss with hospital specialist

Adverse effects	Action
Sore throat / mouth ulcers / fever / pallor	Arrange urgent FBC. Consider stopping dapsone and contacting hospital specialist.
Abnormal purpura / bruising / bleeding / jaundice	**Stop dapsone** and discuss with hospital specialist. Arrange urgent FBC, coagulation screen, LFT.
Methaemoglobulinaemia: Light-headedness / headache / fatigue / dyspnoea / bluish skin or lips / chest pain	Immediately discuss with hospital specialist. Check observations and serum methaemoglobin levels. Patient may require hospital admission if unstable.
Dapsone hypersensitivity reaction (widespread rash, pruritus, fever, lymphadenopathy, peripheral eosinophilia) - usually within first 6 weeks of starting dapsone	**Stop dapsone** and immediately discuss with hospital specialist. Check observations and arrange urgent FBC, LFT, U+E.

Notable Drug Interactions (Refer to BNF and SPC)

This list is not exhaustive; for additional information and further interactions, consult the BNF and Summary of Product Characteristics [https://www.medicines.org.uk/emc/product/5768/smpc].

- Anti-epileptics (fosphenytoin, phenytoin, phenobarbital, primidone) – use with caution due to increased risk of side effects
- Anti-malarials (chloroquine, primaquine) – use with caution due to increased risk of side effects
- Clozapine – contraindicated due to the risk of blood dyscrasias
- Folic acid antagonists (e.g. methotrexate) – increase dapsone levels with increased risk of side effects
- Nitrofuratoin – use with caution due to increased risk of side effects
- Saquinavir – contraindicated due to the risk of cardiac arrhythmias
- Probenicid – increases dapsone levels with increased risk of side effects
- Rifampicin and rifabutin – use with caution as decrease dapsone levels
- Sulphonamides – use with caution due to increased risk of haemolysis
- Trimethoprim and co-trimoxazole – increase dapsone levels with increased risk of side effects. Increased risk of dapsone toxicity (methaemoglobinaemia).

Back-up Information and Advice

On call dermatology specialty registrar (9am – 9pm) or on call dermatology consultant (overnight)	Via OUH switchboard (01865 741166)
Dermatology secretaries at Churchill Hospital, Oxford	01865 228224 (9am – 5pm)
Dermatology secretary at Horton hospital, Banbury	01295 229683

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