Shared Care Guideline

Sulfasalazine - in rheumatic diseases

Executive Summary
- Sulfasalazine is used as a disease-modifying agent to induce and maintain remission of rheumatoid arthritis (RA).
- Enteric-coated tablets are recommended to reduce the risk of adverse drug reactions.
- The starting dose is 500mg once a week, increasing by 500mg per week to a dose of 1G twice a day (or higher if clinically appropriate).
- Clinical response usually starts within approximately 3 months.
- Sulfasalazine is usually considered safe in pregnancy (maximum dose 2g/day, folic acid 5mg daily supplementation for the mother) and in breastfeeding of a healthy full-term infant.
- Sulfasalazine can be prescribed to men of childbearing potential although there may be transient reversible oligospermia. Conception may be enhanced by stopping sulfasalazine for 3 months prior to conception.
- Most adverse drug reactions occur within 6 months of starting treatment. Some undesirable effects are dose-dependent and symptoms may be alleviated by dose reduction.
- The most common adverse drug reactions are nausea, headache, rash, loss of appetite and raised temperature.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. 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. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here
1. **Scope**
Cross-boundary: Trust and general practice in adult patients.

2. **Aim**
To provide guidance in the use of sulfasalazine as a disease-modifying agent in the treatment of rheumatoid arthritis.

3. **Introduction**
Sulfasalazine is used as a disease modifying agent to induce and maintain remission in rheumatoid arthritis and psoriatic arthritis. It is potentially toxic and therefore the drug must be monitored, particularly in the first three months of treatment. This shared care guideline outlines the responsibility of primary and secondary care clinicians using sulfasalazine in rheumatic diseases.

4. **Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALT</td>
<td>alanine transaminase</td>
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<tr>
<td>DMARD</td>
<td>disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FBC</td>
<td>full blood count</td>
</tr>
<tr>
<td>G-6-PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner</td>
</tr>
<tr>
<td>LFTs</td>
<td>liver function tests</td>
</tr>
<tr>
<td>MCV</td>
<td>mean cell volume</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell count</td>
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</table>

5. **Dose and Administration**
Sulfasalazine 500mg enteric coated tablets are recommended as gastrointestinal intolerance is more likely to occur with plain tablets.

- The starting dose is 500mg daily for one week, increasing by 500mg each week up to a maximum of 2gm daily. This is usually taken in two divided doses (1g twice a day).
- Higher doses may be used if required, for example 1g three times a day. Very occasionally the dose may exceed 3g daily.
- Clinical response usually starts in approximately three months.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/10722).
6. Adverse Effects

About 75% of adverse drug reactions occur within 3 months of starting therapy, and over 90% by 6 months. Some undesirable effects are dose-dependent and symptoms can often be alleviated by reducing the dose.

Common (≥1/100 to < 1/10);

Blood disorders; cough; dizziness; fever; Heinz body anaemia; insomnia; megaloblastic anaemia; proteinuria; pruritus; stomatitis; taste disturbances; tinnitus, nausea vomiting, abdominal discomfort, headache, anorexia

Uncommon (≥1/1000 to < 1/100).

Alopecia; convulsions; depression; dyspnoea; vasculitis, rash including Stevens Johnson Syndrome

Further information can be found in the British National Formulary and the Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/10722).

7. Cautions

- Sulfasalazine should not be prescribed for patients with known impaired hepatic or renal function or with blood dyscrasias unless the benefits outweigh the risks.
- Patients must be warned to report a sore throat or signs of bruising / bleeding.
- Sulfasalazine should not be prescribed for patients with known G-6-PD deficiency because of the risk of haemolytic anaemia.
- Sulfasalazine can cause folic acid deficiency potentially resulting in serious blood disorders (e.g., macrocytosis and pancytopenia). Supplementation with folic acid or folinic acid may be required.
- Sulfasalazine may cause crystalluria and kidney stone formation. Adequate fluid intake should be ensured during treatment.
- Hypoglycemia may occur in patients receiving sulfonamides including sulfasalazine due to chemical similarity with some oral hypoglycaemic agents. Close monitoring of blood glucose is required in patients with diabetes mellitus.
- Sulfasalazine should be used with caution in patients with severe allergy or bronchial asthma.
- If sulfasalazine is used in pregnancy, the dose must not exceed 2g/day and folate supplements should be given to the mother due to the risk of folate deficiency (folic acid 5mg daily).
- Sulfasalazine can be prescribed to men of childbearing potential although there may be transient reversible oligospermia. Conception may be enhanced by stopping sulfasalazine 3 months prior to conception.
Sulfasalazine is split by intestinal bacteria to sulfapyridine and 5-amino salicylate so adverse drug reactions to either sulfonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience adverse drug reactions related to sulfapyridine.

Annual influenza vaccination is recommended.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/10722) and in Rheumatology: Rheumatology Advance Access (Jan 2016) ‘BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids’ http://rheumatology.oxfordjournals.org/content/early/2016/01/12/rheumatology.kev404.full

8. Contraindications
   - Known hypersensitivity to sulfasalazine and its metabolites
   - Known hypersensitivity to sulfonamides or salicylates.
   - Patients with porphyria.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/10722).

9. Interactions
   Digoxin: absorption of digoxin may be reduced leading to sub-therapeutic levels.
   6-Mercaptopurine and Azathioprine: increased risk of bone marrow suppression and leucopenia
   Methotrexate: increased risk of gastrointestinal adverse effects.
   Sulfonamides: Increased risk of hypoglycemia

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

| Pre-treatment by the hospital rheumatology team. | Check ESR, FBC, creatinine/calculated GFR, ALT and/or AST and albumin |

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Initiation to stabilisation monitoring by the hospital rheumatology team (or GP if in agreement).

- Check ESR, FBC, creatinine/calculated GFR, ALT and/or AST and albumin every:
- Two weeks until on stable dose for 12 weeks then
- Once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months
- Thereafter FBC, creatinine/calculated GFR, ALT, and/or AST and albumin at least every 12 weeks*
- Look out for downward trends as well as absolute levels of blood counts.

On-going monitoring by GP once stable.

- ESR, FBC, LFTs, U&Es once every three months.
- If dose and monitoring are stable after one year, blood monitoring can be reduced to every six months.
- Ask about rash and oral ulceration at each visit.

Legend: ESR: erythrocyte sedimentation rate; FBC: full blood count; LFTs: liver function tests; RFTs: renal function tests; U&Es: urea and electrolytes.

All results to be recorded in a patient-held record.

The following table includes advice on what action to take if test results rise or fall below defined limits or if the patient reports one of the adverse events below:

<table>
<thead>
<tr>
<th>Test results</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>Leucopaenia WBC &lt; 3.5 x10⁹/L, or</td>
<td><strong>STOP SULFASALAZINE</strong> and inform rheumatologist or rheumatology practitioner: see contact list below</td>
</tr>
<tr>
<td>Neutropenia &lt; 1.5 x10⁹/L, or</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia platelets &lt;150 x10⁹/L, or</td>
<td></td>
</tr>
<tr>
<td>LFTs &gt; 2 x upper limit of normal (ULN)</td>
<td></td>
</tr>
<tr>
<td>MCV &gt; 105fl</td>
<td>Check B12, folate and TSH levels. If abnormal, treat any underlying abnormality. If normal, discuss with the hospital rheumatology team.</td>
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<table>
<thead>
<tr>
<th>Symptoms/side effects</th>
<th>Action</th>
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<tbody>
<tr>
<td>Abnormal bruising/ bleeding or severe sore throat</td>
<td>Check FBC immediately and withhold sulfasalazine until results available. Discuss with specialist team if necessary.</td>
</tr>
<tr>
<td>Fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness</td>
<td>Check FBC and LFTs immediately and withhold sulfasalazine until results available. Discuss with specialist team if necessary.</td>
</tr>
</tbody>
</table>
• Significant infection: Urgent FBC looking for neutropaenia. If present, withhold sulfasalazine and discuss with specialist team.

• Unexplained acute widespread rash: Stop sulfasalazine and seek urgent specialist advice – preferably dermatological.

• Oral ulceration: Withhold sulfasalazine and discuss with specialist team.

• Nausea, dizziness, headache: If possible, continue sulfasalazine. May have to consider dose reduction, or stop sulfasalazine if symptoms are severe. Discuss with the hospital rheumatology team.

**Legend:** LFTs: liver function tests; MCV: mean cell volume; ULN: upper limit of normal; WBC: white blood cell count.

### 11. Shared Care Responsibilities

**a. Hospital specialist:**
- Send a letter to the GP requesting shared care for the patient. Agreement to shared care will be assumed unless GP advises otherwise.
- Ensure accurate details of patient’s prescription are communicated.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- Provide any advice to the patient/carer when requested.
- Initiate treatment and prescribe the first month of treatment.
- Routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose and most recent test results are stated.
- Evaluate any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Ensure that backup advice is available at all times.

**b. General Practitioner:**
- Agree to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Monitor patient’s overall health and well-being.
- Prescribe the drug treatment as described.
- Monitor blood results (ESR, FBC, LFTs, RFTs, U&Es) in line with recommendations from hospital specialist.
- Help in monitoring the progression of disease.

**c. Patient or parent/carer:**
- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
• Do not exceed the recommended dose.
• Patients must attend their scheduled test appointments to assist health professionals to provide effective, safe, appropriate treatment.
• Inform other clinical staff that they are receiving treatment.
• Report any adverse effects to the hospital specialist or GP.
• Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
• Share any concerns they have in relation to treatment with sulfasalazine.

12. Contact numbers for advice and support

<table>
<thead>
<tr>
<th>Cambridge University Hospital NHS Foundation Trust</th>
<th>Post</th>
<th>Telephone</th>
</tr>
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<tbody>
<tr>
<td>Medicines Information department</td>
<td></td>
<td>01223 217502</td>
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**Rheumatology Department**
Decisions to alter or discontinue treatment are usually discussed via the Rheumatology Helpline on 01223 254933. The on-call rheumatology specialist registrar (SpR) may also be contacted via the Addenbrooke’s Contact Centre.

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Post</th>
<th>Telephone</th>
</tr>
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<tbody>
<tr>
<td>Jill Bloxham; Julie Isaacson; Tracey Nash, Jane How</td>
<td>Rheumatology practitioners</td>
<td>01223 254933, option 3</td>
</tr>
<tr>
<td>Dr G Clunie, Dr FC Hall, Dr D Jadon, Dr N Jordan, Dr M Lillicrap, Dr A Malaviya, Dr A Negoescu, Dr K Poole, Dr J Rees, Dr N Shenker</td>
<td>Consultant rheumatologist</td>
<td>01223 254933, option 4</td>
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13. Monitoring compliance with and the effectiveness of this document
Specialties will regularly review their incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly.

14. Equality and Diversity Statement
This document complies with the Cambridge University Hospital NHS Foundation Trust service Equality and Diversity statement.

15. Disclaimer
It is your responsibility to check that this printed out copy is the most recent issue of this document.


<table>
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<th>Document ratification and history</th>
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<tr>
<td>Approved by:</td>
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<td>Date approved:</td>
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<td>Submitted for ratification by:</td>
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Owning Provider Trust: Cambridge University Hospital NHS Foundation Trust
Version number: 4

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/10722) and in Rheumatology: Rheumatology Advance Access (Jan 2016) ‘BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids’ http://rheumatology.oxfordjournals.org/content/early/2016/01/12/rheumatology.kev404.full