Results
Case study 45:
DMARDs in rheumatoid arthritis

January 2007
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Case study 45: DMARDs in rheumatoid arthritis

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decision based on this information should be made in the context of the clinical circumstances of each patient. Declarations of interest have been sought from all commentators.
Scenario
Anita, aged 62, has a 15-year history of rheumatoid arthritis (RA) characterised by morning stiffness and widespread symmetrical joint swelling (hands, wrists, feet, elbows, knees and shoulders). Aurothiomalate injections started by her rheumatologist controlled her symptoms for 10 years. Oral methotrexate was started 3 years ago with modest response. Leflunomide was added, but ceased after 3 weeks due to severe skin reaction. Since then, the RA has been reasonably controlled on escalating doses of oral methotrexate, folic acid and prednisone, with occasional intra-articular corticosteroids. Paracetamol/codeine 500/30 mg tablets were taken when required. Aspirin hypersensitivity precluded use of nonsteroidal anti-inflammatory drugs.

When Anita was reviewed by her rheumatologist 3 months ago, synovitis was noted (swollen and tender joints), blood review revealed elevated C-reactive protein (CRP, 41 mg/L), mildly elevated erythrocyte sedimentation rate (ESR, 22 mm/h), but otherwise normal electrolytes and LFTs. She received methylprednisolone injection into several joints. Her oral methotrexate dose was increased to 20 mg every Monday, and prednisone to 15 mg daily. Because of nausea associated with methotrexate, folic acid was increased to 2.5 mg daily (except Mondays). Sulfasalazine 1 g twice daily was also added and she continues to take 1–2 tablets of paracetamol/codeine 500/30 mg when the pain is severe.

Anita presents today with worsening morning stiffness in her wrists and feet. She is finding housework more difficult, has not been sleeping well and had to cancel an overseas trip because of the pain. Synovitis is evident in her metacarpophalangeal and proximal interphalangeal joints, she has some hair loss and a blood review last month shows further elevation of CRP.

Other current medications are raloxifene 60 mg daily (osteoporosis) and polyvinyl alcohol 3% eye drops when required (dry eyes).

1. a) Should Anita be considered for a biological disease-modifying antirheumatic drug (DMARD)?
   □ Yes □ No
   b) Why/why not? Explain using history and current findings.
   i. ____________________________________________
   ii. ____________________________________________
   iii. ____________________________________________
   iv. ____________________________________________

Two months later ...
Anita’s rheumatologist commences her on adalimumab (Humira) 40 mg subcutaneous injection every 2 weeks. She is taught how to self-administer the injections. Her previous medications are continued but prednisone has been reduced to 5 mg daily. Her rheumatologist refers her back to the GP for ongoing monitoring and care.
2. **What should be monitored during treatment with adalimumab, and how often?**

<table>
<thead>
<tr>
<th>Monitoring parameter</th>
<th>How often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td></td>
</tr>
<tr>
<td>ii.</td>
<td></td>
</tr>
<tr>
<td>iii.</td>
<td></td>
</tr>
<tr>
<td>iv.</td>
<td></td>
</tr>
</tbody>
</table>

3. **How should Anita’s response to her current RA medications be assessed?**

i.  

ii. 

iii.  

iv.  

4. **What advice should Anita receive regarding all her current RA medications?**

i.  

ii.  

iii.  

iv.  
Summary of results

At the time of publication, 903 responses had been received. Responses from 200 general practitioners have been compiled for feedback.

Case synopsis
A 62-year-old patient with a 15-year history of rheumatoid arthritis is currently managed on methotrexate 20 mg every Monday, sulphasalazine 1 g twice daily and prednisone 15 mg daily. Other medications are folic acid 2.5 mg (daily except Mondays), paracetamol/codeine 500/30 mg (1–2 tablets when required for severe pain), occasional intra-articular corticosteroids, raloxifene (60 mg daily) and polyvinyl alcohol 3% eye drops (when required). Despite current treatment, the patient presents with worsening disease activity and functional impairment. She is also experiencing hair loss. (See page 3 for more details.)

Considering use of a biological DMARD

• 97.5% of respondents would consider using a biological disease-modifying antirheumatic drug (DMARD) because of:
  — inadequate response to (95.4%), and adverse effects from conventional DMARDs (15.4%)
  — raised C-reactive protein (CRP) concentration (45.6%)
  — clinical findings and indicators suggesting progressing disease and/or poor outcomes in rheumatoid arthritis (RA), e.g. involvement of large number of joints (26.2%), persistent synovitis (21.5%), significant functional impairment (20%)
  — lack of other options, e.g. inability to tolerate leflunomide (13.8%)
  — features of biological DMARDs, e.g. improved response when added to methotrexate (8.7%).

• The remaining 2.5% would not consider using a biological DMARD. These respondents suggested increasing the dose of the existing medications and/or trialling the addition of other conventional DMARDs first. Some were also concerned about the toxicities and long-term safety of the biological DMARDs.

Monitoring parameters for adalimumab

• Monitoring parameters for adalimumab recommended by respondents included:
  — conducting a full blood count (87.5%) and liver function tests (79.0%) each month
  — monitoring for signs of heart failure (61.5%) and pulmonary sepsis (53%) at every visit
  — screening for tuberculosis (36.5%) and hepatitis B and C (36%) at baseline
  — screening for reactivated tuberculosis (37%) in the first 2–5 months of treatment.

Assessing response to RA medications

• Parameters for assessing response to the medications included reduced CRP concentration and/or erythrocyte sedimentation rate (ESR) (92.5%), increased functional status (79.5%), reduced duration of morning stiffness (68%), reduced number of affected joints (58.5%), and decreased synovitis (32%).

Advice about RA medications

• Advice given to the patient included information about the need for regular monitoring and follow-up (68%), potential adverse effects and the importance of reporting them (65.5%), the importance of compliance (17.5%), non-pharmacological therapy (12.5%), correct dosing and proper administration of medications (11.5%), and specific advice on adalimumab [e.g. informing the patient that long-term safety is not yet established (11%)].
Results in detail

Considering use of a biological DMARD

- 97.5% of respondents would consider recommending a biological DMARD. Main reasons for this decision are given in Table 1.

<table>
<thead>
<tr>
<th>Reason for considering use of a biological DMARD</th>
<th>% of respondents* (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limitations with current treatment using conventional DMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Inadequate response or no clinical remission (despite high-dose regimen of multiple drugs)</td>
<td>95.4</td>
</tr>
<tr>
<td>Patient experiencing adverse effects (e.g. hair loss from methotrexate, osteoporosis probably from corticosteroid use)</td>
<td>15.4</td>
</tr>
<tr>
<td>Reduce need for high-dose prednisone</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
</tr>
<tr>
<td>Raised CRP concentration and/or other biological markers</td>
<td>45.6</td>
</tr>
<tr>
<td><strong>Clinical findings and/or presence of indicators of poor RA outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Severe disease</td>
<td>27.2</td>
</tr>
<tr>
<td>Involvement of a large number of joints (&gt; 20 joints), including small joints</td>
<td>26.2</td>
</tr>
<tr>
<td>Persistent synovitis</td>
<td>21.5</td>
</tr>
<tr>
<td>Significant functional impairment</td>
<td>20.0</td>
</tr>
<tr>
<td>Worsening symptoms</td>
<td>13.8</td>
</tr>
<tr>
<td>Persistent morning stiffness</td>
<td>10.8</td>
</tr>
<tr>
<td>Impaired quality of life</td>
<td>10.8</td>
</tr>
<tr>
<td>Persistent pain</td>
<td>9.2</td>
</tr>
<tr>
<td>Long duration of disease</td>
<td>6.7</td>
</tr>
<tr>
<td>Risk of irreversible damage</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Lack of other options</strong></td>
<td></td>
</tr>
<tr>
<td>Patient unable to tolerate leflunomide</td>
<td>13.8</td>
</tr>
<tr>
<td>Options exhausted and remaining DMARDs unlikely to help</td>
<td>8.7</td>
</tr>
<tr>
<td>Patient unable to take aspirin and non-steroidal anti-inflammatory drugs</td>
<td>6.2</td>
</tr>
<tr>
<td><strong>Features of biological DMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Combination of biological DMARD with methotrexate can improve response</td>
<td>8.7</td>
</tr>
<tr>
<td>Biological DMARD generally well tolerated</td>
<td>3.6</td>
</tr>
<tr>
<td>No contraindications (for this patient)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Respondents may have more than one response

- The remaining 2.5% would not consider using a biological DMARD. These respondents suggested increasing the dose of Anita’s existing medications (methotrexate, sulfasalazine) and/or trialling the addition of other conventional DMARDs (hydroxychloroquine, leflunomide) first. Some were also concerned about the toxicities and long-term safety of the biological DMARDs.
Practice points

- Biological DMARDs should be considered for the treatment of RA if remission is not achieved with the appropriate use of conventional DMARDs\(^1\) or if conventional DMARDs cannot be tolerated.
- Combining a biological DMARD with methotrexate provides greater efficacy compared with methotrexate alone.\(^2,5\)
- The Schedule of Pharmaceutical Benefits\(^6\) lists the criteria for initial PBS-subsidised treatment with a biological DMARD; Anita’s case is worked through as an example in Table 2.

| Table 2. Criteria for initial PBS-subsidised treatment with a biological DMARD |
|---------------------------------|---------------------|---------------------|
| **Criterion**                   | **Anita’s example** |
| Adult                           | ✓                   |
| Severe active RA                | ✓                   |
| Received no prior PBS-subsidised treatment with a bDMARD for this condition in this treatment cycle | ✓ |
| Failed to achieve an adequate response to the following treatments: | |
| (i) Methotrexate ≥ 20 mg weekly, AND | (i) ✓ (methotrexate 20 mg weekly) |
| (ii) Methotrexate ≥ 7.5 mg weekly, in combination with 2 other conventional DMARDs, for ≥ 3 months, AND | (ii) ✓ (methotrexate with prednisone\(^7\) and sulfasalazine for ≥ 3 months) |
| (iii) ≥ 3 months treatment with: | (iii) severe skin reaction to leflunomide after 3 weeks’ treatment |
| — leflunomide alone; OR | |
| — leflunomide and methotrexate; OR | |
| — cyclosporine | |
| If treatment with any of the above-mentioned drugs is contraindicated according to the TGA-approved product information, or if intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use, the patient is exempted from demonstrating an inadequate response to that particular agent(s) only. | |
| Failure to achieve adequate response indicated by: | |
| ESR > 25 mm/h OR CRP >15 mg/L, AND | ✓ (CRP 41 mg/L) |
| (i) ≥ 20 active (swollen and tender) joints, OR | ✓ (probably) |
| (ii) ≥ 4 active joints from the following list of major joints: | |
| — elbow, wrist, knee and/or ankle (assessed as swollen and tender), and/or | |
| — shoulder and/or hip (assessed as pain and restriction in passive movement due to active disease, not irreversible damage) | ✓ (shoulders) |

\(^*\)From Schedule of Pharmaceutical Benefits\(^6\); all criteria have to be met

\(^\dagger\) For the purposes of PBS subsidy of biological DMARDs for rheumatoid arthritis, Medicare Australia (personal correspondence, 6 December 2006) has advised that prednisolone at doses of ≥ 7.5mg daily is accepted as a DMARD.
Monitoring parameters for adalimumab

• This question was interpreted in two ways. Most respondents answered it in terms of monitoring for the potential toxicities associated with adalimumab — these responses are summarised in Table 3. Some respondents also answered the question with respect to monitoring response to adalimumab therapy — these responses are included in Table 5.

Table 3

<table>
<thead>
<tr>
<th>Monitoring parameters (frequency of monitoring*)</th>
<th>% of respondents† (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count [FBC] (monthly for first 6 months, then at increased intervals thereafter)</td>
<td>87.5</td>
</tr>
<tr>
<td>Liver function tests [LFTs] (monthly for first 6 months, then at increased intervals thereafter)</td>
<td>79.0</td>
</tr>
<tr>
<td>Signs of heart failure or other cardiac abnormalities (at every visit)</td>
<td>61.5</td>
</tr>
<tr>
<td>Signs of pulmonary sepsis or other lung abnormalities (at every visit)</td>
<td>53.0</td>
</tr>
<tr>
<td>Reactivated tuberculosis (in the first 2–5 months of treatment)</td>
<td>37.0</td>
</tr>
<tr>
<td>Tuberculosis (at baseline)</td>
<td>36.5</td>
</tr>
<tr>
<td>Hepatitis B and C serology (at baseline)</td>
<td>36.0</td>
</tr>
<tr>
<td>Chickenpox or shingles serology (if exposed during treatment with adalimumab)</td>
<td>16.5</td>
</tr>
<tr>
<td>Adverse drug effects and toxicities, e.g. unspecified infections, neurotoxicity (monthly)</td>
<td>12.5</td>
</tr>
<tr>
<td>Chest X-ray (every 6–12 months)</td>
<td>10.5</td>
</tr>
<tr>
<td>Urea, electrolytes and creatinine (monthly)</td>
<td>10.5</td>
</tr>
<tr>
<td>Injection-site reaction (monthly)</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* Only the most common response has been provided † Respondents may have more than one response

Practice points

• The long-term safety of tumour necrosis factor (TNF) inhibitors such as adalimumab is not yet established and careful monitoring for potential toxicity is an essential part of therapy. In Australia, reported adverse drug reactions involving TNF inhibitors have included pneumonia/lower respiratory tract infections, lupus or lupus-like syndrome, sepsis, anaphylaxis, lymphoma, tuberculosis and malignant melanoma.

• Monitor for injection-site reaction, a common minor adverse event. It may present as mild erythema, itching, pain or swelling, usually lasts for several days, and rarely leads to cessation of therapy.

• Routine monitoring should include the parameters listed in Table 4. Other rare but serious toxicities to be aware of include opportunistic infections (e.g. histoplasmosis, listeriosis), lymphoproliferative disorders, lupus-like syndrome and demyelinating disease.

• Cessation of therapy is recommended if any of the following adverse effects occur while using a biological DMARD: demyelinating disorders, pancytopenia, aplastic anaemia, lupus-like syndrome, worsening heart failure, neoplasia or serious hypersensitivity. Temporary cessation of therapy is recommended in the presence of infection or during surgery peri-operative period.

• The Australian Rheumatology Association (ARA) patient medicine information sheet for adalimumab provides a useful summary of the above-mentioned points. A copy is available in Appendix 1* for photocopying. (ARA patient medicine information sheets for other DMARDs are available from www.rheumatology.org.au/community/PatientMedicineInformation.htm).

*Reproduced with permission of the Australian Rheumatology Association
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B and C serology</td>
<td>Baseline</td>
</tr>
<tr>
<td>Tuberculosis screening</td>
<td>Baseline and during first 2–5 months of treatment</td>
</tr>
<tr>
<td>FBC and LFTs</td>
<td>Monthly for first 6 months, then every 3–6 months (more often if used with other DMARDs)</td>
</tr>
<tr>
<td>Signs of heart failure (in patients with pre-existing heart failure)</td>
<td>Every visit</td>
</tr>
<tr>
<td>Chickenpox or shingles serology</td>
<td>If exposed during treatment</td>
</tr>
</tbody>
</table>

*Adapted from *NPS News* 48: Helping patients achieve remission of rheumatoid arthritis, October 2006*
Assessing response to RA medications

Table 5

<table>
<thead>
<tr>
<th>Response parameters</th>
<th>% of respondents* (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced CRP concentration and/or ESR</td>
<td>92.5</td>
</tr>
<tr>
<td>Increased functional status (e.g. activities of daily living, mobility)</td>
<td>79.5</td>
</tr>
<tr>
<td>Reduced duration of morning stiffness</td>
<td>68.0</td>
</tr>
<tr>
<td>Reduced number of tender and swollen joints</td>
<td>58.5</td>
</tr>
<tr>
<td>Decreased synovitis</td>
<td>32.0</td>
</tr>
<tr>
<td>Decreased pain (e.g. based on pain scores or analgesic requirements)</td>
<td>25.5</td>
</tr>
<tr>
<td>Reduced joint damage as assessed by X-ray</td>
<td>25.0</td>
</tr>
<tr>
<td>Absence of adverse drug effects</td>
<td>23.0</td>
</tr>
<tr>
<td>Improved general clinical picture and reduced symptoms</td>
<td>20.5</td>
</tr>
</tbody>
</table>

* Respondents may have more than one response

Practice points

- Assessing response to medications can be based on disease activity. Review disease activity every 1–3 months until remission is achieved. Remission is defined as symptomatic relief, plus normalisation of inflammatory markers, and the absence of joint swelling.
- Assessing disease activity and response to treatment in RA should include the measures in Box 1.
- In addition to disease activity, response to medications should include monitoring of potential adverse drug reactions (e.g. as discussed in the previous section for adalimumab).

Box 1. Assessment of disease activity and response to treatment in RA

<table>
<thead>
<tr>
<th>Degree of joint pain*</th>
<th>Limitation of function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fatigue</td>
<td>Number of swollen and tender joints</td>
</tr>
<tr>
<td>Duration of morning stiffness</td>
<td>Patient’s global assessment of disease activity*</td>
</tr>
<tr>
<td>ESR and/or CRP concentration</td>
<td>Physician’s global assessment of disease activity*</td>
</tr>
<tr>
<td>Evidence of disease progression (e.g. loss of motion, instability, mal-alignment, deformity and/or structural damage), based on physical examination or radiographic changes</td>
<td></td>
</tr>
</tbody>
</table>

*Usually measured along a visual analogue scale (range 0–10 cm, with higher scores indicating greater severity)
Advice about RA medications

Table 6

<table>
<thead>
<tr>
<th>Advice given to the patient</th>
<th>% of respondents* (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitoring and follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>Emphasise the need for regular monitoring and/or set up a monitoring schedule/reminder</td>
<td>68.0</td>
</tr>
<tr>
<td>Emphasise the need for regular reviews</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Managing potential adverse effects</strong></td>
<td></td>
</tr>
<tr>
<td>Inform the patient about potential adverse effects and the importance of reporting them early</td>
<td>65.5</td>
</tr>
<tr>
<td>Remind the patient to notify the GP immediately of any signs of infection and/or if feeling unwell</td>
<td>24.5</td>
</tr>
<tr>
<td><strong>Self-management and patient involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Discuss the importance of non-pharmacological therapy (e.g. exercise, occupational therapy)</td>
<td>12.5</td>
</tr>
<tr>
<td>Encourage the patient to participate in arthritis self-management courses</td>
<td>6.0</td>
</tr>
<tr>
<td>Encourage the patient to contact Arthritis Australia</td>
<td>5.5</td>
</tr>
<tr>
<td>Provide information on lifestyle measures (e.g. healthy diet)</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Drug dosage and administration</strong></td>
<td></td>
</tr>
<tr>
<td>Remind the patient about correct dosing and proper administration of medications</td>
<td>11.5</td>
</tr>
<tr>
<td>Remind the patient that methotrexate is to be taken once weekly only</td>
<td>6.5</td>
</tr>
<tr>
<td>Reduce the dose of prednisone (gradually)</td>
<td>6.0</td>
</tr>
<tr>
<td>Continue with current medications (i.e. methotrexate, sulfasalazine, prednisone)</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Advice on adalimumab</strong></td>
<td></td>
</tr>
<tr>
<td>Inform the patient that long-term safety is not yet established</td>
<td>11.0</td>
</tr>
<tr>
<td>Inform the patient about rare toxicities (e.g. tuberculosis, demyelinating disease)</td>
<td>10.5</td>
</tr>
<tr>
<td>Report exposure to chicken pox, shingles and/or tuberculosis</td>
<td>8.5</td>
</tr>
<tr>
<td>Monitor for injection-site reactions</td>
<td>5.0</td>
</tr>
<tr>
<td>Maximum response may take up to 1–3 months</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Emphasise the importance of compliance</td>
<td>17.5</td>
</tr>
<tr>
<td>Discuss goal and benefits of therapy (e.g. clinical remission, preventing joint damage)</td>
<td>9.5</td>
</tr>
<tr>
<td>Inform the patient about potential drug interactions and the importance of notifying health professionals of use of any new medications</td>
<td>4.5</td>
</tr>
</tbody>
</table>

* Respondents may have more than one response

Practice points

- Patient information about the disease and its treatment and outcome forms an important part of managing RA.11

- When talking to patients about their RA medications:
  - discuss the goal of therapy and lifestyle interventions
  - provide opportunity and encourage patients to ask questions about their condition and treatment and to be involved in treatment choices
  - explain the importance of using medications strictly as directed
  - advise on symptoms of potential adverse drug reactions and the appropriate course of action
emphasise the importance of regular monitoring and follow-up, and discuss a feasible schedule and reminder system for doing so.

- Practical advice on administration and precautions for adalimumab, methotrexate, sulfasalazine and prednisolone is provided in Table 7.
- The consumer medicine information (CMI) leaflet for each medication also provides useful information, including the indication, directions for use, precautions and potential adverse reactions. Many CMIs can also be downloaded from the NPS website at www.nps.org.au/consumers. A copy of the Humira CMI* for photocopying is included in Appendix 2.

### Table 7. Administration and precautions for adalimumab, methotrexate, sulfasalazine and prednisone¹,⁷,¹³,¹⁴

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Pre-filled syringes should be stored in a refrigerator&lt;br&gt;Rotate injection sites to prevent skin irritation (detailed instructions on administering the injection can be found in the CMI for Humira — see Appendix 2)&lt;br&gt;Keep immunisations up to date (e.g. yearly influenza vaccines) but avoid live vaccines&lt;br&gt;Report exposure to chicken pox or shingles&lt;br&gt;Potential toxicities requiring monitoring are listed on page 8</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Reassure patients that it is effective and generally well tolerated, if the proper precautions are taken&lt;br&gt;Dose to be taken once a week — prevent confusion by providing written information about dose, day and time of administration&lt;br&gt;Dose can be divided into 3 doses given over 24 hours (i.e. at time 0, 12 and 24 hours) if gastrointestinal adverse effects occur&lt;br&gt;Folic acid decreases risk of gastrointestinal adverse effects and liver toxicity; give as a single or split dose, generally not on the same day as methotrexate&lt;br&gt;Parenteral (subcutaneous or intramuscular) methotrexate is an alternative for patients who cannot tolerate oral methotrexate&lt;br&gt;May cause black faecal discolouration&lt;br&gt;May increase skin sensitivity to sunlight — avoid over-exposure and/or use adequate sun protection&lt;br&gt;Potential toxicities requiring monitoring include myelosuppression, abnormal LFTs, hepatotoxicity, nephrotoxicity, interstitial pneumonitis and pulmonary fibrosis</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Contraindicated in patients with hypersensitivity to salicylates or sulfonamides⁷&lt;br&gt;Dose to be taken with food to reduce stomach upset&lt;br&gt;Modified-release preparations should be swallowed whole&lt;br&gt;May impair absorption of folic acid&lt;br&gt;Soft (hydrogel) lenses may be stained; disposable lenses may still be used&lt;br&gt;May cause orange or yellow (in alkaline urine) urine discolouration&lt;br&gt;Potential toxicities requiring monitoring include myelosuppression and abnormal LFTs</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Dose to be taken with or after food, preferably in the morning&lt;br&gt;Medication should not be stopped abruptly</td>
</tr>
</tbody>
</table>

† Anita is taking sulfasalazine despite a documented history of aspirin hypersensitivity (of unspecified severity). This scenario is based on an actual patient who in this case suffered no untoward reaction to sulfasalazine. However, please note that hypersensitivity to salicylate is listed as a contraindication in the product information for all brands of sulfasalazine.

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Commentary 1

Key points

- Rheumatoid arthritis (RA) is a chronic multisystem disease that leads to progressive deformity and loss of function of the joints and is associated with a reduced life expectancy.
- Early diagnosis and treatment with DMARDs are essential in preventing damage and disability.
- The goal of therapy is to achieve clinical remission with minimal toxicity.
- If disease control cannot be achieved with a single agent, combination DMARD therapy should be used.
- In patients with active disease despite combination therapy, biological therapy (especially anti-TNF agents) are indicated.
- Regular clinical review and monitoring are essential.
- Shared care is an important component of optimal management.

Management of RA

RA is a chronic systemic inflammatory disease that causes pain and swelling of joints, ultimately leading to destruction of the joints and the surrounding soft tissues. If the inflammation from RA is unchecked, it may lead to damage of the joint structures, with resultant loss of function and disability. In RA the inflammation primarily affects the joint tissues (synovium) and other joints, but extra-articular features may also occur. The peak onset of disease is within the 4th and 5th decades of life. About half a million Australians suffer from RA.

It is essential to diagnose RA early. The goal of treatment is no longer palliation of symptoms, but rather prevention of the damage the disease causes; therefore prompt treatment must follow early diagnosis.

DMARDs are started early in the disease course with the aim of achieving clinical remission.

Methotrexate is the usual first-line DMARD and is often accompanied by prednisolone, which in low dose in the first 1–2 years of disease may reduce joint damage. The dose of methotrexate is rapidly escalated to a maximum tolerable dose (20–25mg/week) and, unless the activity of the disease is controlled, combination DMARD therapy is then started with other DMARDs added to the methotrexate–prednisolone regimen. Leflunomide is commonly used in combination with methotrexate. Another frequently used combination is methotrexate, sulfasalazine and hydroxychloroquine.

If clinical remission cannot be achieved with combination therapy, a biological agent (especially an anti-TNF agent) is indicated. This may be either etanercept, adalimumab or infliximab. If the patient does not respond sufficiently to an anti-TNF agent, there is some evidence that there may be improved efficacy by switching to another. Biological agents work better in combination with DMARDs, especially methotrexate, so these are usually continued, although there may be some effort to minimise the dosage of conventional DMARDs or, in the case of combination therapy, withdrawing agents and attempting to minimise the dosage of prednisolone.

In all patients with RA, attention must focus on other aspects of their disease. Patients with RA are at increased risk of osteoporosis, both from the disease itself and because prednisolone therapy may contribute to accelerated bone loss. Patients with cardiovascular disease are at increased risk of further cardiovascular, and also renal and hepatic, disease, so close surveillance of blood pressure, renal function and lipid profile is necessary. Patients must be encouraged to stop smoking. Psychosocial factors are also important. RA is associated with depression, and the disease itself can have a significant impact on relationships and the ability
of the patient to work. Regular exercise and an appropriate diet are also important.

It is essential that all patients with RA undergo regular monitoring of disease status, drug toxicity and for comorbidities. This requires shared care between the rheumatologist and the general practitioner and it is important that the patient feels that they are an active partner in the management of their disease.

Managing Anita’s RA

Anita has a long history of RA, which has never been adequately controlled. She has accumulated a significant burden of disease, with several DMARDs proving unsuitable, some because of lack of efficacy, others because of adverse events. She presents now with ongoing synovitis with significant joint pain, aggressive loss of function, disturbed sleep and elevated inflammatory markers. The disease is also beginning to exert a significant effect on her family life. She also has established osteoporosis from her chronic RA, long-term prednisolone therapy and postmenopausal state. She also has secondary Sjögren’s syndrome.

It is encouraging to see that the vast majority of respondents recognise that a biological DMARD (bDMARD) is indicated. Adalimumab was the bDMARD chosen for Anita. Pre-screening for use of bDMARDs requires excluding hepatitis B and C and conditions such as bronchiectasis that may predispose the patient to recurrent infections. Another important condition to exclude is active or, more commonly, latent tuberculosis. It is disappointing that only one-third of respondents recommended pre-screening for tuberculosis. This involves establishing a risk profile and, dependent upon this, QuantiFERON®-TB Gold testing (where available) or Mantoux test and chest X-ray.

Patients with New York Heart Association grade III or IV heart failure are not recommended for bDMARD treatment because of the potential worsening of their heart failure. It is most important to advise patients when they start bDMARD therapy that this treatment may reduce their body’s capacity to fight an infective illness and that they should therefore be vigilant for infections and present to their GP earlier than they would otherwise if they develop a febrile illness. They must also be advised to withhold their bDMARD therapy if they have a fever or infective illness when the next treatment is due. Very few respondents recognised the importance of this advice.

When Anita was started on adalimumab, initially more frequent monitoring would have been necessary. This is to ensure that she was tolerating adalimumab and also to review its efficacy, perhaps with subsequent changes to other DMARD therapies, depending on her response. Some patients may immediately take to self-injecting, others may require education and, after becoming comfortable with injections, undertake these themselves or have a family member administer the injection. Other patients may wish to have injections administered by their GP or the practice nurse.

Anita will require ongoing monitoring of full blood picture, liver function tests, erythrocyte sedimentation rate and C-reactive protein to assess disease activity and toxicity from therapy. With her combination therapies this monitoring should continue monthly. Most respondents identified the importance of this, although suggesting that the interval for testing can be increased after 6 months of therapy.

Almost two-thirds of respondents recommended checking for signs of heart failure at every visit. Anti-TNF agents have been demonstrated to worsen severe heart failure but not induce heart failure in other patients.

Respondents also placed a significant emphasis on routine monitoring for rare but serious toxicities. Since the first clinical use of bDMARDs, international registries have been established and, along with regulatory bodies, have been closely monitoring reports of adverse events. Infective episodes and, in particular, skin infections are more common with bDMARD therapy. Reactivation of latent tuberculosis is associated with bDMARD therapy, more so with infliximab than with etanercept or adalimumab.

There is increased risk of lymphoma in patients with RA, which is related to the severity of disease. As patients with severe disease are more likely to receive bDMARDs, reports of lymphoma associated with their use are currently felt to reflect this factor rather than a direct effect of the anti-TNF agents.

International surveillance for long-term toxicities
is essential and ongoing but there is no place for routine monitoring of such problems in an individual patient.

It is most important that patients receiving combination, and especially bDMARD, therapy for their RA undergo regular monitoring and follow-up. It was therefore disappointing that only 17% of respondents emphasised the need for regular review.

It is most important that both the patient and the doctor remain vigilant for signs of infection in patients using bDMARDs. However, only 24.5% of respondents would remind Anita to notify her GP immediately with signs of infection.

Anita has a 15-year burden of insufficiently controlled RA. This has taken its toll on her joints and has led to significant loss of function and disability. This is now having significant psychosocial implications. It is important that this aspect of RA is considered. A low percentage of respondents would give specific advice to Anita regarding self-management of her condition. Exercise, diet and self-management courses such as those run by the state arthritis organisations are an important part of the management of patients with chronic RA.

**Recommendations for Anita**

Anita has chronic RA and combination DMARD therapy has failed, so adalimumab has been started as an anti-TNF agent. I would recommend:

- Pre-screening for latent TB, hepatitis B and C
- Thorough explanation of the nature of adalimumab therapy and the importance of:
  - regular monitoring
  - surveillance for infections and withholding a due injection if febrile or an infection is present.
  - seeking prompt medical attention if febrile or unwell.
- Explanation that after 3 months of therapy efficacy will be assessed and therapy will be continued only if there has been sufficient improvement.
- After clinical improvement, aiming to minimise the dosage of prednisolone and in the medium term considering withdrawing sulfasalazine but continuing methotrexate therapy
- Considering changing raloxifene to an oral bisphosphonate for better management
- Reinforcing the importance of diet and exercise
- Participation in an arthritis self-management program
- Ensuring that the psychological and social impact of the disease is considered.
Commentary 2

Key points

- Rheumatoid disease requires early diagnosis, referral and consideration for optimal treatment to prevent irreversible disability.
- Rheumatoid arthritis (RA) is a complex multisystem disease, not just arthritis, and thus requires multidisciplinary care.
- GPs have the tools to co-ordinate this care by optimal use of the GP Management Plan and Team Care additions.
- GPs need to continue to develop their capabilities in care co-ordination and maintain awareness of current treatment options.

Monitoring parameters for RA

About 438,000 Australians have RA, predominantly older women. While not a prime cause of mortality, it is a major cause of morbidity, pain and disability as well as shortened life expectancy (mortality ratio 1.98–3.08); 44.3% of RA patients will die from cardiovascular disease and another 18.3% from cancer.

Early diagnosis is the key to optimal management. Maximal effective care is imperative not only in newly detected cases, but also for the larger cohort of patients with varying maintenance therapies. Many are denied access to tertiary referral centres or appropriate specialist care by virtue of rurality, ethnicity, cultural factors and other contributors to social deprivation. Maintaining ‘best practice’ among treating physicians is a challenge. Most family physicians have only a handful of regular patients with RA and will be the point of first diagnosis only 2-3 times in a lifetime of practice. From the 2001 National Health Survey, the most common health professionals consulted by RA patients were (in order of frequency) chemists, physiotherapists/hydrotherapists, chiropodists/ podiatrists, chiropractors and nurses. GP consultations were less than 3% of the total.

Also, in 2003-04, RA accounted for 0.3% of all problems managed by GPs.

Although awareness of the new anti-TNF-α therapies was high (97.5%), respondents’ supervision and monitoring suggestions were less than optimal. Only 53% expressed concerns regarding signs of pulmonary sepsis or other lung abnormalities and only 37% intended to examine for reactivated tuberculosis. While it is reasonable to assume that the initiating specialist should have screened for active TB, hepatitis B and C at baseline, this should be confirmed by sighting the report.

Monthly request for FBE, electrolytes and LFTs is inadequate and not useful alone. Responsible monitoring entails regular skin review for pallor, petechiae, purpura and infections such as erysipelas and cellulitis, as well as checking the injection site for reactions. A thorough examination of the respiratory system should be performed, as well as using the best GP tool of them all, adequate history taking, checking for low-grade fever, dyspnoea, cough, weight loss and headache. The fivefold increase in lymphoma risk observed with Humira (note there is a several-fold increased risk in untreated RA alone, especially in more severe disease) cannot be easily detected by routine blood testing, nor can the occasional development of a reversible lupus-like syndrome. A good case can be made for regular micro-urines and/or office-based screening with urinary catalase testing. The main diatheses to detect are pneumonia, septic arthritis, skin infections, diverticulitis and pyelonephritis. An annual chest X-ray could easily be justified.

Respondents should be commended for their attention to the cardiovascular system in view of the mortality statistics for RA as well as the small incidence of chronic heart failure in the trials with other TNF inhibitors. There is little evidence of harm in the preliminary trials in regard to renal function or liver disease, with only 4% expressing rises in transaminase levels. Cytopenia is similarly rare.
Assessing response

Again it appears that there may be an over-dependence on blood testing to assess response. RA is a complex multisystem disease that is not just diagnosed by a positive rheumatoid factor, and response is not as simple as seeing reductions in CRP levels. The Australian Rheumatology Association protocol involves a full assessment of global response by a Disease Activity Score including a 28-joint count (DAS28). This is based on the number of tender (t28) and swollen joints (sw28) as well as the patient’s visual analogue scale (VAS) score of global disease activity, not just by a simple haematological marker of inflammation:

\[
\text{DAS28} = [0.56 \sqrt{t28}] + [0.28 \sqrt{sw28}] + [0.70 \ln(ESR)] + [0.014 VAS]
\]

Assessing response incompletely potentially enables continuation of an ineffective, expensive and possibly harmful intervention. For more information on using DAS28, see www.das-score.nl.

The GP Management Plan

Now an accepted model in general practice, this should entail preparing and describing all planned reviews, including clinical, diagnostic pathology and radiology assessments, and their frequency. Ideally it should be developed in close consultation with the treating rheumatologist or tertiary outpatients and have the recall and review procedure outlined. The GP’s role in detecting infection or markers of malignancy and managing cardiovascular risk factors should be defined. There should be time for regular discussion of the goals and benefits of therapy.

Incidental approaches may be mentioned, such as steroid injection of troublesome joints as an office procedure, but use caution, as the usual ‘no touch’ technique may not be adequate. Consider extra sterile precautions during joint injections when patients are using TNF inhibitors.

The Team Care addition

Care of complex disease is no longer a burden to be shouldered by the primary care practitioner. The team approach is reinforcing and self-empowering. In RA almost every arm of the health profession can contribute. The pharmacist can be a formidable ally in the quest for compliance, appropriate use of planned therapies and monitoring of adverse effects. Home Medicines Review by a clinical pharmacist may reveal possible polypharmacy and drug interactions, especially from unexpected sources. The practice nurse may provide a source of accessible advice and support. Physiotherapy and occupational therapy input is essential for joint protection and muscular rehabilitation. Discuss use of chiropractic therapies and, if necessary, assess odontoid and alar ligament integrity radiologically. The podiatrist assists in detecting and managing deformities and pressure areas. Dietitians can minimise the negative protein balance, cardiovascular risk factors in the diet and maximise potentially beneficial agents such as fish oils. The dentist can minimise dental harm from salivary gland dysfunction, as Sjogren’s disease is commonly associated with RA. Also, temporo-mandibular joint dysfunction can contribute to the dietary difficulties facing RA patients.

The most common referral from GPs is to rheumatologists. However, this is happening too infrequently, too late and, when it does occur, there seems to be too little involvement and communication with the co-ordinating GP.

The second most common referral from GPs for RA patients is to orthopaedic surgeons. It is critical for preservation of activities of daily living that restorative surgery is appropriately offered, especially in regard to hand function, but also for major joint replacement.

It was disconcerting to see that only 6% of respondents considered referral to Arthritis Australia or to a self-management course, an acknowledged and valued intervention.
Further advice

In Anita’s case there should be a continued attempt to achieve steroid reduction. This may be facilitated by a time-contingent approach to analgesic dosing with judicious use of paracetamol ± codeine. The potential for bowel and neurological side effects needs to be kept in mind. Deficiency in iron transport is common and oral iron sources should be estimated. Vitamin C taken before meals may enhance iron absorption. Preservation of bone density could be achieved by maximising calcium and vitamin D intake and incorporating load-bearing exercise when possible.

Although raloxifene may offer a degree of protection from breast cancer28 there is little evidence that this will protect Anita’s peripheral skeleton from fracture,29 and bisphosphonate therapy should be considered.

Depression commonly accompanies RA. Psychosocial factors such as loss of paid employment, marital breakdown and loss of a positive body image are all frequent contributors. Non-drug therapies, including relaxation, breathing methods, tai chi and other mind–body therapies, should be considered.

However, as Anita is suffering sleep disturbance, lowered coping ability and lifestyle impact, pharmacological therapy needs consideration. This could include s-adenosyl methionine (SAMe), in view of this nutrient’s performance compared with tricyclic antidepressants30 and its pain-relieving capacities relative to celecoxib.31 Interactions between SSRIs and tramadol or dextropropoxyphene are important to detect, as well as considering the potential cardiotoxic effects of tricyclics.

Above all, the GP should realise the prime importance of maintaining the thread of continuity during the ongoing care of this complex condition.
**What is Adalimumab?**

Adalimumab (brand name Humira®) belongs to a new class of medicines called *biological disease modifying antirheumatic drugs* (bDMARDs).

These medicines block natural substances called cytokines, which are found in excessive amounts in the blood and joints of people with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

The increased levels of cytokines cause inflammation, which results in symptoms of pain, joint swelling and stiffness, and can lead to joint damage.

By blocking the cytokine called Tumour Necrosis Factor (TNF), Adalimumab reduces inflammation, lessens the symptoms and helps stop further joint damage.

**What benefit can you expect from your treatment?**

Unlike many standard DMARDs, Adalimumab works relatively quickly and some relief of joint swelling, pain and stiffness may be noticed within the first 4 weeks of treatment.

If Adalimumab treatment is stopped for more than a few weeks there is a risk that your condition will get worse again. Continue with your treatment unless advised by your doctor or unless side effects develop.

Current Australian prescribing restrictions for all bDMARDS mean Adalimumab will not be started if your rheumatoid arthritis is not active or if standard treatments, including Methotrexate, have not been tried first.

It will also not be continued unless the response is adequate. Response will be assessed between 12 and 16 weeks.

**How is Adalimumab given?**

Adalimumab is injected under the skin of the abdomen or thighs.

It can be injected by your doctor, nurse or carer, or by you. If injecting yourself, be sure to follow the detailed instructions carefully to ensure the best response. It is particularly important to change the injection site each time.

The medicine must also be kept refrigerated.

The usual dose for adults is 40mg once every two weeks.

Adalimumab may be used with other arthritis medicines including:

- other DMARDs such as Methotrexate;
- steroid medicines such as prednisolone or cortisol injections into the joint;
- anti-inflammatory medicines (NSAIDs) such as naproxen or ibuprofen; and/or
- simple pain killers such as paracetamol.

It cannot be given with other biological DMARDs.

**Are there any side effects?**

bDMARDs have now been given to over half a million people worldwide since initial use in the late 1990s.

Overleaf are side effects that you might experience with your treatment. Tell your doctor if you experience any side effects.
Most common side effects:

- Up to 30% of people receiving Adalimumab have mild pain, swelling or itching at the site of the injection. This can be reduced by applying ice and antihistamine and steroid creams to the injection site.
- Headaches, cough and stomach and bowel discomfort may also occur.
- As Adalimumab affects the immune system, mild infections, particularly of the upper respiratory tract (colds, sinusitis and flu) may occur more frequently than usual.

Less common or rare side effects:

- Serious infections such as Tuberculosis (TB) are seen rarely and screening for TB is needed before treatment begins (see below).
- Rarely Adalimumab may cause an allergic reaction with itchy, red skin or a rash or a feeling of tightness in the chest and difficulty breathing.
- Side effects involving the nerves, such as inflammation of the nerve to the eye, may also occur rarely.
- Very rarely ‘drug-induced lupus’ has occurred with symptoms of rash, fever and increased joint pain. This usually disappears when Adalimumab treatment is stopped.
- Cancer: There seems to be no increased risk of cancer, but this is still unclear. Lymphoma, a cancer of lymph glands, is found more commonly in patients with persistent active rheumatoid arthritis than in the general population. Studies are in progress to see if Adalimumab changes this.
  If cancer has been previously treated and cured it is unclear whether a bDMARD can be used safely. At present an interval of 5-10 years is recommended between cure of a cancer and starting bDMARDs.

What precautions are necessary?

Tests prior to commencing treatment:

- Adalimumab cannot be given if you have tuberculosis (TB) or HIV infection, as it is likely to make these conditions worse.
- If you have latent (inactive) TB, preventative anti-TB treatment will be started 4 to 6 weeks before Adalimumab. The anti-TB treatment may need to be taken for up to 9 months.
- Hepatitis B or C infection also present a risk in this regard, but may not necessarily exclude treatment.
- The following tests are therefore required before commencing treatment with Adalimumab:
  - blood tests for Hepatitis B and C;
  - chest x-ray and two step Tuberculin Skin Test (Mantoux) or QuantiFERON assay for tuberculosis (TB).
- HIV tests are required only for those who are at risk of this infection.
- If you have an active infection of any kind, treatment with Adalimumab will not be given until the infection is treated successfully.

Ongoing blood tests:

- Blood tests will also be required during your treatment to monitor your condition and to determine the effectiveness of treatment.
- The frequency of blood tests will depend on what other medicines you are taking and what other illnesses you might have. Your rheumatologist will determine the frequency of tests required.

Other diseases:

- Due to the possible effects of Adalimumab on the nerves, it cannot be given to people with multiple sclerosis.
- It should not be given to people with moderate to severe heart failure.
- It should not be given to people with systemic lupus erythematosus (lupus/SLE).
Surgery:
- If you require surgery for any reason, treatment with Adalimumab will be stopped prior to surgery. It will be restarted again after the operation at a time determined by your surgeon and rheumatologist.
- Treatment will only be restarted once the wound is healed and if there is no infection present.

Vaccines:
- Most vaccines can be given safely with Adalimumab, however live vaccines, such as measles vaccine, should not be given. Flu vaccines and Pneumovax are safe and recommended.

Pregnancy and breastfeeding:
- Until more is known about its effects on the unborn baby, you should not take Adalimumab if you are or plan to become pregnant.
- You should also avoid breastfeeding if taking the medicine.

All patients taking Adalimumab should be seen regularly by a rheumatologist to optimise treatment and to minimise any potential side effects.

If you have any questions or concerns write them down and discuss them with your doctor.

Your doctor’s contact details:

REMEMBER – Keep all medicines out of reach of children
HUMIRA
Adalimumab

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Humira.

It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you using Humira against the benefits they expect it will have for you.

If you have any concerns about using this medicine, ask your doctor or pharmacist.

Read this leaflet carefully before you use Humira and keep it with the medicine. You may need to read it again.

What Humira is used for

Humira is used to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis, a painful disease of the joints, as well as slow down and protect against damage to joints. Signs and symptoms of rheumatoid arthritis include joint pain, tenderness, swelling and stiffness.

Humira is also used to reduce the signs and symptoms of moderately to severely active psoriatic arthritis, a disease of the joints and skin, with some similarities to rheumatoid arthritis, as well as psoriasis and other factors.

Humira is also used to reduce the signs and symptoms in patients with active ankylosing spondylitis, an inflammatory disease of the spine. Signs and symptoms of ankylosing spondylitis include back pain and morning stiffness.

The active ingredient in Humira is adalimumab, a fully human monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which collects in your joints, and may cause your rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.

If you have moderately to severely active rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis, you may be first given other disease modifying medicines, such as methotrexate, sulfasalazine, or hydroxychloroquine. If you do not respond well enough to these medicines, you may be prescribed Humira to reduce the signs and symptoms of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis as well as to slow down and protect against the damage to your joints.

Ask your doctor if you have any questions about why this medicine has been prescribed for you. Your doctor may have prescribed it for another reason.

Humira is not recommended for use in children, as there have been no studies of its effects in children.

This medicine is available only with a doctor’s prescription.

Before you use Humira

When you must not use it

Do not use Humira if you have:
1. An allergy to any medicine containing adalimumab or any of the ingredients listed at the end of this leaflet.
2. A severe infection including sepsis, active tuberculosis and opportunistic infections.
3. You are already using anakinra – a medicine for rheumatoid arthritis.
4. You have moderate to severe heart failure.

Symptoms of an allergic reaction may include:
- chest tightness
- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- hives, itching or skin rash

Do not use this medicine after the expiry date printed on the label/blister/carton or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start using this medicine, talk to your doctor.

Before you use it

Tell your doctor if you have allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any of the following medical conditions:
- an infection, including a long-term or localised infection (for example, leg ulcer)
- other severe infections (for example sepsis, opportunistic infections or tuberculosis (see below))
- a history of recurrent infections or other conditions that increase the risk of infections
- you are a carrier of or you suspect you may be infected with the hepatitis B virus
- a fungal infection
- multiple sclerosis and other demyelinating disease
- congestive heart failure, cancer or autoimmune disease
- kidney or liver problems
- you experience allergic reactions such as chest tightness, wheezing, dizziness, swelling or rash
- tuberculosis, or if you have been in close contact with someone who has had tuberculosis
- a suppressed immune system
- allergic to rubber or latex

As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical history, a chest x-ray and tuberculin test.

Tell your doctor if you are pregnant or plan to become pregnant.
The effects of Humira in pregnant women are not known. Therefore the use of Humira in pregnant women is not recommended.

Tell your doctor if you are breastfeeding or plan to breastfeed.
It is not known whether Humira passes into breast milk. If you are breastfeeding, your doctor may advise you to stop breastfeeding while you are using Humira.

If you have not told your doctor or pharmacist about any of the above, tell them before you start using Humira.

Taking other medicines
Tell your doctor or pharmacist if you are taking any other medicines, including any that you get without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and Humira may interfere with each other. Your doctor and pharmacist have more information on medicines to be careful with or avoid while using this medicine.

Tell your doctor or pharmacist if you are taking anakinra, as the combination with Humira may increase the risk of infection. You should not take Humira and anakinra together.

Humira can be taken together with medicines used to treat arthritis, such as: methotrexate, steroids or pain medications including non-steroidal anti-inflammatory drugs.

How to use Humira

Follow all directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet.

If you do not understand the instructions on the label or in this leaflet, ask your doctor or pharmacist for help.

How much to use
Always use Humira exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose for adults with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis is one injection fortnightly. Your doctor may prescribe other medicines for rheumatoid or psoriatic arthritis to take with Humira.

How to use it
Humira is injected under the skin. The injection can be self-administered or given by another person, for example a family member or friend after proper training in injection technique, or your doctor or his/her assistant.

Instructions for preparing and giving an injection of Humira:
The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed in the same syringe or vial with any other medicine.

1. Setting up
- Wash your hands thoroughly
- Set up the following items on a clean surface
  - One pre-filled syringe of Humira for injection.
  - One alcohol pad.
- Look at the expiry date on the syringe. Do not use the product after the month and year shown. Check the colour has not changed and that there are no particles in the solution.

2. Choosing and preparing an injection site
- Choose a site on your
  - Thigh
  - Stomach
- Each new injection should be given at least 3 cm from the last injection site.
  - Do not inject in an area where the skin is tender, reddened, bruised, or hard.
This may mean there is an infection.
- Wipe the injection site with the enclosed alcohol pad, using a circular motion.
- Do not touch the area again before injecting.

3. Injecting Humira
- Remove the cap from needle syringe, being careful not to touch needle or let it touch any surface.
- With one hand, gently grasp the cleaned areas of skin and hold firmly.
- With the other hand, hold syringe at 45-degree angle to skin, with the grooved side up.
- With one quick, short motion, push needle all the way into skin
- Release the skin with the first hand
- Push plunger to inject solution – it can take from 2 to 5 seconds to empty the syringe.
  \- **Patient:** When the syringe is empty, remove the needle from skin, being careful to keep it at the same angle as when it was inserted
  \- **Health Professional/Caregiver:** Hold the syringe in one hand and with the other hand slide the outer protective shield over the protective needle until it locks in place.
- **Patient/Health Professional/Caregiver**
  Using cotton wool or a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. Do not rub the injection site. Use a band-aid if you want to.

4. Throwing away supplies
- **NEVER** re-use the Humira syringe. This product is for one dose in one patient only.
- **NEVER** re-cap a needle.
- After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep this container out of the reach of children.

**How long to use it**
Humira will not cure your condition but should help control arthritic pain, swelling and stiffness.

**Keep using Humira for as long as your doctor tells you.**

**If you forget to use it**
If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then inject your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

Do not give yourself two injections to make up for the injection that you missed.

If you are not sure what to do, ask your doctor or pharmacist.

**If you use too much (overdose)**
If you accidentally inject Humira more frequently than told to by your doctor, immediately telephone your doctor or the Poisons Information Centre (Australia: Telephone 13 11 26; New Zealand: Telephone 0800 764 766), or go to Accident and Emergency at your nearest hospital. Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention. Always take the outer carton of the medicine with you.

**Side effects**
Check with your doctor as soon as possible if you have any problems while using Humira, even if you do not think the problems are connected with the medicine or are not listed in this leaflet.

Like all medicines, Humira can cause some side effects.

Ask your doctor or pharmacist any questions you may have.

Tell your doctor if you notice any of the following:
- Upper respiratory tract infections
- Headache
- Rash

**While you are using Humira**

**Things you must do**
Count with your doctor before you receive any vaccines. Some vaccines, such as oral polio vaccine, should not be given while receiving Humira.
- Injection site pain / redness / bleeding
- Nausea
- Diarrhoea
- Sore throat
- Drowsiness
- Trouble sleeping
- Agitation
- Depression
- Dizziness
- Shaking or tremors
- Eye, ear and taste disorders
- Chest pain
- Changes in the way your heart beats eg if you notice it beating faster
- Bruising or increased bleeding
- Abdominal pain
- Constipation
- Tooth and tongue disorder
- Changes in the way your skin feels and looks

Tell your doctor if you notice anything that is making you feel unwell, even if it is not on this list.

**After using Humira**

**Storage**

Keep your pre-filled syringe in the pack until it is time to use it.

Keep Humira in a refrigerator (2°C-8°C). Do not freeze.

Keep Humira in the refrigerator in a way children cannot get to it.

Do not leave Humira in the car especially in hot weather.

**Disposal**

After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.

If your doctor tells you to stop using Humira or the expiry date has passed, ask your pharmacist what to do with any medicine that is left over.

**Ingredients**

- Active ingredient: 40 mg adalimumab

- Other ingredients:
  - Mannitol
  - Citric acid monohydrate
  - Sodium citrate
  - Monobasic sodium phosphate dihydrate
  - Dibasic sodium phosphate dihydrate
  - Sodium chloride
  - Polysorbate 80
  - Water for injections

**Distributor**

Humira is distributed in Australia by:
Abbott Australasia Pty Ltd
ABN 95 000 180 389
32-34 Lord St
Botany NSW 2019

Humira is distributed in New Zealand by:
Abbott Laboratories (NZ) Ltd
4 Pacific Rise
Mt Wellington
NEW ZEALAND

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Version 02

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Tell your doctor immediately if you notice any of the following:

- Persistent cough, weight loss, listlessness, fever
- Serious infection. Signs of an infection may include fever, wounds, feeling tired or dental problems.
- Nerve disorders
- Feeling weak or tired
- Coughing
- Tingling
- Numbness
- Double vision
- Arm or leg weakness

If any of the following happen, tell your doctor immediately or go to Accident and Emergency at your nearest hospital:

- Severe rash
- Swollen face
- Trouble breathing

Other side effects not listed above may occur in some people.

Do not be alarmed by this list of possible side effects. You may not get any of them.

**What it looks like**

Humira is a clear, colourless, sterile solution of 40mg adalimumab in 0.8mL water in a syringe. The following packs are available:

- Pre-filled syringe for patient use in packs containing 1 or 2 pre-filled syringes with 1 or 2 alcohol pads (AUST R 95780)

- Pre-filled syringe with needle guard for hospital administration or administration by a caregiver, in packs containing 1 pre-filled syringe with 1 alcohol pad (AUST R 95781)
References


