Adalimumab (Humira) for axial spondyloarthritis – second line

May 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Adalimumab (Humira) for axial spondyloarthritis – second line

Target group
- Axial spondyloarthritis: treatment of signs and symptoms in spondyloarthritic adult patients with axial manifestation – second line, after failure of non-steroidal anti-inflammatory drugs (NSAIDs) due to non-response or intolerance.

Background
Spondyloarthritis (SpA) is a heterogenous group of overlapping chronic inflammatory rheumatologic diseases. It can be divided into five subsets; ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease-associated arthritis, reactive arthritis and undifferentiated SpA (uSpA). These diseases all share common genetic, histologic and clinical characteristics such as a high prevalence of HLA-B27, synovitis, as well as involvement of the axial and peripheral skeleton. Alternatively SpA can be divided into diseases with predominately axial involvement (i.e. sacroiliac joints and/or spine) or predominantly peripheral manifestations (i.e. peripheral arthritis, enthesitis and dactylitis). The term axial SpA includes AS and uSpA without radiographic sacroiliitis, but with clinically predominant axial involvement. It is often used to describe the early stages of axial inflammation before the development of radiographic sacroiliitis and possible AS diagnosis.

Technology description
Adalimumab (Humira, D2E7) is a fully human recombinant monoclonal antibody directed against tumour necrosis factor alpha (TNFα). Currently there are several TNFα inhibitors already on the market for the treatment of AS. Adalimumab is intended for the treatment of the signs and symptoms in spondyloarthritic adult patients with axial manifestation after the failure of NSAIDs due to inadequate response or intolerance. Adalimumab is presented in a pre-filled syringe or pen and administered via the subcutaneous (SC) route at 40mg given every other week as a monotherapy. As axial spondyloarthritis is a chronic condition long-term therapy is likely to be required to maintain control of the disease.

Adalimumab is licensed for:
- Rheumatoid arthritis: moderate to severe, active – second line, after failure of disease-modifying anti-rheumatic drugs (DMARDs) in combination with methotrexate or as monotherapy in case of intolerance to methotrexate, or when continued treatment with methotrexate is inappropriate.
- Rheumatoid arthritis: severe, active and progressive – first line in combination with methotrexate or as monotherapy in case of intolerance to methotrexate, or when continued treatment with methotrexate is inappropriate.
- Polycyclic juvenile idiopathic arthritis: active – second line, after failure of DMARDs in children and adolescent patients aged 4 to 17 years in combination with methotrexate or as monotherapy in case of intolerance to methotrexate, or when continued treatment with methotrexate is inappropriate.
- Psoriatic arthritis: active, progressive – second line, after failure of DMARDs.
- AS: severe, active – second line after failure of conventional therapy.
- Crohn’s disease: severe, active – second line after failure of corticosteroids and/or immunosuppressants, or in patients who are intolerant to or have medical contraindications for such therapies.
• Psoriasis: moderate to severe – second line after failure of systemic therapy or in patients who have a contraindication to, or are intolerant to other systemic therapies.

Common adverse effects reported during clinical studies using adalimumab include: injection site reactions, respiratory tract infections, leucopenia, headache, abdominal pain, nausea, vomiting, rash, musculoskeletal pain, abnormal liver enzymes and raised blood lipids.

Adalimumab is in phase III development for Crohn’s disease in paediatric patients, ulcerative colitis, uveitis, paediatric enthesitis-related arthritis, peripheral spondyloarthritis and paediatric psoriasis.

Innovation and/or advantages
If licensed, adalimumab would provide a treatment for adult patients with spondyloarthritis with axial manifestation who have failed to respond or who are intolerant to NSAIDs, where treatment options are currently limited.

Developer
Abbott Laboratories.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The Musculoskeletal Services Framework (2006).

Relevant guidance
• NICE technology appraisal in development. Ulcerative colitis (moderate to severe, second line) – adalimumab. Expected date of issue to be confirmed.
• NICE technology appraisal. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. 2010.
• NICE technology appraisal. Use of tumour necrosis factor alpha (TNF-a) inhibitors (adalimumab and infliximab) for Crohn's disease (review of TA40). 2010.
• NICE technology appraisal. Adalimumab, etanercept and infliximab for ankylosing spondylitis. 2008.
• NICE technology appraisal. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. 2007.
• Assessment of Spondyloarthritis International Society and European League Against Rheumatism (ASAS/EULAR) recommendations for the management of ankylosing spondylitis. 2006.
Clinical need and burden of disease

An estimated 2% of patients each year present to General Practice with back pain, and up to 5% of these will show features of AS. SpAs as a group are one of the most common rheumatic diseases with a prevalence of 0.5-1.9%, making them roughly as common as rheumatoid arthritis. The most common SpA subgroups are AS and uSpA. NICE estimate the prevalence of clinically significant AS at 0.15% of the population with an annual incidence of 6.9 per 100,000, representing approximately 2,300 new cases each year in England and Wales. AS is more common in men than women, with men more likely to develop severe spinal disease. About a third of people with AS may be unable to work altogether, with a further 15% reporting some changes to their working lives. Patients with AS have an increased mortality risk, with a standardised mortality ratio of ≥1.5. Causes of death include cardiovascular disease, amyloidosis and fractures.

Existing comparators and treatments

Short-term and long-term treatment goals for SpA include minimising pain and stiffness, maintaining function and posture, and arresting radiographic progression. The management of SpA should be individualised according to the patient’s clinical presentation, comorbidities and wishes. Guidelines have been published for the management of AS. These guidelines suggest a combination of patient/family education, exercise, physical therapy and surgery, as well as pharmacological treatments.

Pharmacological therapies for AS include:
- NSAIDs – first line.
- Analgesics – for patients in whom NSAIDs are insufficient, contraindicated and/or poorly tolerated.
- Corticosteroid injections to local musculoskeletal inflammation site.
- DMARDs – no evidence for efficacy in axial disease, but may be considered in patients with peripheral arthritis.
- Anti-TNFα treatment – given to patients with persistently high disease activity.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00235105; adults; adalimumab or placebo; phase II/III.</th>
<th>NCT00939003; adults; adalimumab or placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Charite University, Berlin, Germany.</td>
<td>Abbott Laboratories.</td>
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<tr>
<td>Status</td>
<td>Completed.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, publication.</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>Germany.</td>
<td>EU (inc. UK), USA, Canada and Australia.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled, double arm.</td>
<td>Randomised, placebo-controlled, double arm.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=46; adults; moderate to severely active axial spondyloarthritis without radiological sacroilitis; MRI indicating acute inflammatory spine lesions or positive HLA-B27; poor response to ≥1 NSAID; chronic back pain with onset &lt;50 years of age. Randomised to adalimumab SC 40mg or placebo, given every other week for up to 12 weeks. After week 12 all patients can receive adalimumab SC.</td>
<td>n=194 (planned); adults; axial spondyloarthritis; MRI indicating active sacroilitis or positive HLA-B27; poor response to ≥1 NSAID; chronic back pain with onset &lt;45 years of age. Randomised to adalimumab SC 40mg or placebo, given every other week for up to 12 weeks. After week 12 all patients can receive adalimumab SC.</td>
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patients can receive adalimumab SC open label 40mg every other week until week 52 (40 weeks for placebo group).

open label 40mg every other week until week 104.

<table>
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<tr>
<th>Follow-up</th>
<th>Initial treatment period 12 weeks, maintenance therapy up to week 52. Subsequent follow up for 24 weeks.</th>
<th>Initial treatment period 12 weeks. Follow up 116 weeks.</th>
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<tbody>
<tr>
<td>Primary outcomes</td>
<td>ASAS(^a) 40 improvement criteria(^b) response at week 12.</td>
<td>ASAS 40 improvement criteria response at week 12; adverse events (AEs).</td>
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<tr>
<td>Secondary outcomes</td>
<td>ASAS 20(^c) and 70; BASDAI(^d) 20, 50 and 70; BASFI(^e) (absolute change from baseline); mobility examinations; DC-ART20(^f); inflammatory blood markers (CRP, ESR); quality of life questionnaire (SF-36, EQ-5D, NRS); enthesitis index (Maastricht scale); swollen joint count; safety.</td>
<td>At week 12: ASAS 20 improvement criteria; ASAS partial remission(^g), ASAS 5/6 improvement criteria(^h); BASDAI50(^i).</td>
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<tr>
<td>Key results</td>
<td>All patients completed 12 week trial, 38 patients (83%) completed extension to week 52. At week 12, for adalimumab and placebo groups respectively: ASAS 40 response, 54.5% vs 12.5% (p=0.004); ASAS 20 response, 68.2% vs 25% (p=0.007); ASAS partial remission response, 22.7% vs 0% (p=0.019). At week 52, for adalimumab 52 week and adalimumab 40 week groups respectively: ASAS 40 response, 45.5% vs 54.2% (p=0.004); ASAS 20 response, 54.5% vs 66.7% (p=0.002); ASAS partial remission response, 18.2% vs 37.5% (p=0.002).</td>
<td>-</td>
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<td>Expected reporting date</td>
<td>-</td>
<td>August 2012.</td>
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<td>Adverse effects (AEs)</td>
<td>By week 12, 123 AEs had been reported in 40 patients; 63 AEs in 19 patients and 60 AEs in 21 patients in adalimumab and placebo groups respectively. Common AEs included respiratory and skin infections. No serious AEs occurred.</td>
<td>-</td>
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</table>

\(^a\) ASAS - Assessment of Spondyloarthritis International Society.
\(^b\) ASAS 40 Improvement criteria - Improvement of >40% and >2 unit in at least 3 of 4 domains on a scale of 10. Domains include spinal pain, patient global condition, overall health and functional activity.
\(^c\) ASAS 20 Improvement criteria - Improvement of >20% and >1 unit in at least 3 of 4 domains on a scale of 10.
\(^d\) BASDAI - Bath Ankylosing Spondylitis Disease Activity Index.
\(^e\) BASFI - Bath Ankylosing Spondylitis Functional Index.
\(^f\) DC-ART 20 - disease controlling antirheumatic therapy.
\(^g\) ASAS partial remission - A value not above 2 units in each of the 4 domains on a scale of 10.
\(^h\) ASAS 5/6 Improvement criteria - Improvement of >20% in at least five domains. Additional domains include spinal mobility and C-reactive protein (CRP).
Estimated cost and cost impact

The cost of adalimumab for axial SpA is not yet known. However, adalimumab for the treatment of AS costs £357.50 for 40mg. The following anti-TNFα drugs are recommended for the treatment of severely active AS in patients after failure of NSAIDs due to non-response or intolerance:

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Period: 1 yr</th>
<th>Cost</th>
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</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>40mg every other week.</td>
<td>£9,295</td>
<td></td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>50mg once weekly.</td>
<td>£9,296</td>
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</table>

Claimed or potential impact – speculative

Patients
- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

Services
- Increased use
- Decreased use
- Service organisation
- Staff requirements
- Other: None identified

Costs
- Increased unit cost compared to alternative
- New costs:
  - Increased costs: more patients coming for treatment
  - Increased costs: capital investment needed
  - Savings:
  - Other:
- None identified

Other issues
- Clinical uncertainty or other research question identified:
  - The natural history of axial SpA is not fully understood. The role of this medication in combination with existing immunosuppressants and other DMARDs has not been established.
- None identified

References


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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon