THE TREATMENT OF RHEUMATOID ARTHRITIS

Biologicals for rheumatoid arthritis

Peter Tugwell,1 Jasvinder A Singh,2 George A Wells3

The term biological describes treatments developed and produced in live cell systems. The drugs may also be referred to as biological therapies or cytokine modulators.1 By targeting molecules involved in the inflammatory response, such as tumour necrosis factor-α, some biologicals help to reduce or suppress inflammation, potentially reducing joint damage in rheumatoid arthritis. They are used for an increasing number of indications and are approved in some countries for conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn’s disease, and ulcerative colitis. Most of these conditions are autoimmune diseases characterised by upregulation of cytokines such as interleukins; tumour necrosis factor and T and B lymphocytes contribute to the inflammation, a central pathophysiological feature of these conditions. The following are approved for treatment of rheumatoid arthritis in the United Kingdom or the United States, or both:

- Five tumour necrosis factor inhibitors: adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade)
- Anti-interleukin 1 therapy: anakinra (Kineret)
- T cell costimulator modulator: abatacept (Orencia)
- Anti-CD20 therapy: rituximab (Rituxan or MabThera)
- Anti-interleukin 6 receptor therapy: tocilizumab (marketed as RoActemra in Europe and Mexico, and as Actemra in other countries).

Box 1 explains how traditional disease modifying antirheumatic drugs (DMARDs) work compared with biologicals.

How do the biologicals compare with other drugs?

Recent guidelines from the National Institute for Health and Clinical Excellence (NICE), based on a systematic review and considerations of cost effectiveness, recommend that in addition to low dose glucocorticoids, two trials of six months of traditional DMARD monotherapy or combination therapy (at least one including methotrexate) should fail to control symptoms or prevent disease progression before a biological is recommended.1

Consensus recommendations from the American College of Rheumatology and the European League Against Rheumatism,1 also based on systematic reviews, give similar advice. In patients with low clinical, radiological, and serological activity, they recommend use of biologicals only in patients for whom traditional DMARDs (monotherapy or combination therapy, including methotrexate, leflunomide, hydroxychloroquine, sulfasalazine or hydroxychloroquine; and inhibition of T lymphocytes with ciclosporin. In contrast, several of the biologicals have more specific cytokine targets—for example, inhibition of tumour necrosis factor-α with etanercept, adalimumab, infliximab or of interleukin 6 with tocilizumab. Two anticipated advantages with the new biologicals were improved clinical efficacy and halting of joint destruction in combination with DMARDs, and a better safety profile.

Box 1: Mechanisms of action: traditional DMARDs versus biologicals

Traditional disease modifying antirheumatic drugs (DMARDs) are medications such as methotrexate, sulphasalazine, and hydroxychloroquine that modify the underlying systemic inflammatory process of rheumatoid arthritis by their impact on synovitis and bone and joint destruction. Traditionally this response manifested as improvement in swollen and painful joints, improvement in erythrocyte sedimentation rate (a marker of inflammation), and slowing of radiographic progression. In contrast, medications such as non-steroidal anti-inflammatory drugs provide symptomatic relief but do not alter the course of the condition. The various mechanisms of action of DMARDs include inhibition of purine or pyrimidine synthesis with methotrexate, azathioprine, and lefunomide; induction of apoptosis of inflammatory cells with sulphasalazine or hydroxychloroquine; and inhibition of T lymphocytes with ciclosporin. In contrast, several of the biologicals have more specific cytokine targets—for example, inhibition of tumour necrosis factor-α with etanercept, adalimumab, infliximab or of interleukin 6 with tocilizumab. Two anticipated advantages with the new biologicals were improved clinical efficacy and halting of joint destruction in combination with DMARDs, and a better safety profile.

CASE SCENARIO

A 45 year old woman had seropositive erosive rheumatoid arthritis diagnosed three years ago with involvement of the hands, wrists, shoulders, and feet. She found it difficult to dress, cook, do the housework, and control her dog on her morning walk. She improved initially on triple disease modifying antirheumatic drug (DMARD) therapy (methotrexate 25 mg intramuscularly weekly with oral folic acid 1 mg daily, hydroxychloroquine 400 mg daily, sulphasalazine 1 g twice daily) and naproxen 500 mg twice daily. Her symptoms have now flared up despite continuation of triple DMARD therapy, with multiple swollen and tender joints. Radiographs show that since last year she has developed new erosions in her metacarpophalangeal joints. She wants to discuss the new biological drugs that you mentioned would be an option if she did not respond to the above therapy.

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.
<table>
<thead>
<tr>
<th>ACR 50</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>3.25 (2.02 to 5.22)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>3.91 (2.61 to 5.86)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1.79 (0.92 to 3.49)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>5.27 (2.95 to 9.41)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>5.18 (2.92 to 9.18)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>3.13 (1.74 to 5.62)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2.94 (1.64 to 5.27)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>4.44 (2.27 to 8.69)</td>
</tr>
<tr>
<td>Tobtocilizumab</td>
<td>5.61 (3.35 to 9.40)</td>
</tr>
<tr>
<td>Overall</td>
<td>3.81 (3.06 to 4.73)</td>
</tr>
</tbody>
</table>

Fig 1 | Comparison of each biological drug with placebo for benefit (ACR 50). Data adapted from Singh et al. All trials meeting the eligibility criteria and using the doses approved by the US Food and Drug Administration were included as specified in the methods of the Cochrane overview. The longest follow-up in truly blinded phase was used.

### How well do biologicals work?

We recently published a Cochrane network meta-analysis of 27 studies containing 7643 patients taking six biologicals (abatacept, adalimumab, anakinra, etanercept, infliximab and rituximab). We did an adjusted indirect comparison using a generalised mixed model approach. For this article we have updated this to include all nine biologicals (40 studies containing 12161 patients).

As shown in figure 1 and the table, in patients with an inadequate response to methotrexate, compared with placebo the use of biologicals was associated with a number needed to treat of three in achieving an “ACR 50” improvement (defined as a 50% improvement in patient and physician reported criteria of the American College of Rheumatology—see footnote in table for fuller definition). Each biological was significantly more likely than placebo to achieve an ACR 50 (fig 1). Five year observational registry data show that over five years 30% of patients discontinue tumour necrosis factor inhibitors, but those who continue taking the biological maintain the degree of ACR 50 benefit over the five years.

Remission (elimination of all symptoms and signs) occurs rarely. Prevention of irreversible joint destruction is generally thought to be a major potential benefit of biologicals in rheumatoid arthritis, and although controlled trials report only one year of radiographic data, these show a relative effect of 66% (2.44/3.7 × 100) reduction in radiographic progression. This is only a small absolute reduction (<1%) as the scale is 0-440 over 26 joint areas. However, as joint destruction in only a few joints may lead to disability, a reduction by two thirds is potentially of great importance. One model attempts to put this in clinical terms by transforming radiographic scores into estimates of irreversible physical disability, expressed as units from the health assessment questionnaire (HAQ) extrapolated over 10 years: thus for a 10 year period, the biologicals would prevent an increase in disability of 0.34 out of 3.0 (11.3%) irreversible HAQ units, over and above the clinical benefit.

### Summary of findings from Cochrane reviews of biologicals for rheumatoid arthritis (values adjusted for control event rate)**††

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Corresponding risk with intervention (biological)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Number needed to treat for benefit or harm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 50 improvement†</td>
<td>All biologics</td>
<td>Control</td>
<td>Mean difference score 2.44 lower (3.37 to 1.5 lower)</td>
<td>Mean ratio 2.94 (1.68 to 11.21)††</td>
<td>4199 (11)</td>
<td>Moderate§§</td>
<td>Extrapolated over 10 years: additional benefit of 0.34 (11.3%) irreversible HAQ disability units§</td>
</tr>
<tr>
<td>Radiographic progression over 1 year (mean change in score†)</td>
<td>Five biologics§</td>
<td>Control</td>
<td>Mean score 3.7 higher</td>
<td>Odds ratio 3.81 (3.06 to 4.73)</td>
<td>12 161 (40)</td>
<td>Moderate#</td>
<td>3 (3 to 4)</td>
</tr>
<tr>
<td>Withdrawals because of adverse events</td>
<td>All biologics‡</td>
<td>Control</td>
<td>125 (103 to 151) per 1000</td>
<td>Odds ratio 1.32 (1.06 to 1.64)</td>
<td>43 506 (131)</td>
<td>Moderate¶¶</td>
<td>37 (19 to 190)</td>
</tr>
<tr>
<td>Tuberculosis reactivation</td>
<td>All biologics‡</td>
<td>Control</td>
<td>20 per 10 000</td>
<td>Odds ratio 4.68 (1.18 to 18.60)</td>
<td>31 524 (73)</td>
<td>Low***</td>
<td>681 (143 to 17 060)</td>
</tr>
</tbody>
</table>

*For four of the biologicals (adalimumab, etanercept, infliximab, and golimumab) the studies involved patients who had never taken methotrexate before; for these patients, the effect estimates compared with placebo were reduced but were still significant, and comparisons among the four biologicals were similar. The American College of Rheumatology (ACR) criteria are indicated as ACR 20, ACR 50, and ACR70, to reflect 20%, 50%, or 70% improvement in tender or swollen joint counts and the same level of improvement in three of the following five areas: acute phase reactant (such as sedimentation rate); patient's overall assessment; physician's overall assessment; pain scale; disability,functional questionnaire. ACR 50 is used in the Cochrane reviews as best representing clinically important improvement. In both the intervention and control groups, the dose of prednisone (<7.5 mg a day) was unchanged, and no constraints were placed on any single or non-steroidal anti-inflammatory drugs.

†Modified total Sharp score divided by Sharp van der Heijde score (0-440): increase in score means increased joint damage.

‡Abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab. All trials meeting the eligibility criteria and using the doses approved by the US Food and Drug Administration as specified in the methods. We used the longest follow-up in the truly blinded phase.

§Adalimumab, certolizumab, etanercept, infliximab, tocilizumab.

¶Placebo, plus (in patients with incomplete response to methotrexate) unchanged dose of methotrexate.

**Data derived from countries where tuberculosis is endemic as well as from those where tuberculosis is not endemic, so rates might be lower in the latter.

††Based on the 95% confidence interval of the mean difference, the mean ratio could be as low as 1.68 or as high as 11.21 relative to the control mean of 3.7.

‡‡Randomisation methods not described in 18 studies; intention to treat analysis not done in four studies; allocation concealment not clearly described in 12 studies; blinding not described in 10 studies; attrition not clear in one study; and ≥20% drop out in one study.

§§Randomisation methods not described in three studies; allocation concealment not clearly described in one study; and blinding not described in three studies.

¶¶The 95% confidence interval around the pooled effect includes both no effect and appreciable benefit or harm.

***Few events (12 cases in 31 524 patients overall, with 25 cases in 20 976 patients with rheumatoid arthritis).
from the improvement in the reversible components of the ACR 50. This exceeds the accepted level of minimal clinically important change of 0.22 HAQ units, though the model makes a number of simplifying assumptions.

**How safe are the new biologicals?**

Our group also conducted a Cochrane review and network meta-analysis of 163 randomised controlled trials with 50010 participants and 46 extension studies with 11954 participants. This included data on biologicals from 63 (39%) of the trials and 18 (39%) of the extension studies in rheumatoid arthritis and from 100 trials and 28 extension studies of other conditions (ankylosing spondylitis, cancer, inflammatory bowel disease, psoriasis, and other similar conditions). The results did not differ substantively in the patients with rheumatoid arthritis compared with the others but provided more precise estimates.

Overall, compared with placebo, biologicals were associated with significantly higher rates of total adverse events, withdrawals because of adverse events, and reactivation of tuberculosis. After adjustment for dose, biologicals as a group were associated with an absolute 3% higher rate of withdrawals because of adverse events (number needed to harm 37; 95% confidence interval 19 to 190; fig 2 and the table) and an increased absolute 0.2% a year risk of reactivation of tuberculosis (681; 143 to 14706); this estimate varies between countries where tuberculosis is endemic and those where it’s not, and probably between ethnic and social groups.

On limited data, we examined the previously reported possible adverse events of lymphoma and congestive heart failure; these were not significantly different for biologicals and control treatment. However, biologicals are relatively new, and insufficient time has elapsed to enable detection of rare or delayed serious events associated with them. For example, several cases of progressive multifocal leukoencephalopathy (caused by the John Cunningham virus, which infects over 80% of humans) have been reported in patients treated with rituximab.

**What are the precautions?**

When considering treatment with a biological, precautions are necessary in patients with certain conditions (such as severe infections or risk factors for these) and after administration of certain live virus vaccines. Box 2 outlines these precautions in more detail.

**How are the new biologicals taken and monitored?**

All biologicals are parenteral so far. Routes of administration can differ (such as intravenous infusion over two to three hours or subcutaneous injections that can be self-administered), as can frequencies of doses (daily to every three hours or subcutaneous injections that can be self-administered). Monitor patients frequently initially, until the minimal target of remission or low disease activity is reached, and then no less often than every three to four months, with C reactive protein and key measures of disease activity.

**Box 2 | Precautions when prescribing biologicals**

- Do not prescribe biologicals in patients with severe infections such as sepsis (to avoid the risk of worsening sepsis), abscess, active tuberculosis, opportunistic infections; moderate or severe (NYHA class III and IV respectively) congestive heart failure (to avoid risk of worsening symptoms); or multiple sclerosis (to avoid risk of further demyelination)
- Identify for pretreatment counselling and infection reduction strategies those with:
  - Known risk factors for sepsis, such as neutropenia alone or in association with Felty’s syndrome
  - Coexistent diabetes
  - Bronchiectasis
  - Diverticular disease
  - Immunoglobulin deficiency
- Perform a tuberculin skin test or blood tests for tuberculosis, plus chest radiography if indicated—for example, if the skin test or blood test give equivocal or positive results
- Avoid starting biologicals within three months of administration of the following live virus vaccines:
  - BCG
  - Typhoid (oral)
  - Cholera (oral)
  - Measles
  - Mumps
  - Rubella
  - Oral poliomyelitis (Sabin)
  - Yellow fever
  - Varicella
  - Rotavirus
  - Japanese encephalitis (advised by the UK’s Department of Health)
- Check serology for hepatitis B before using rituximab (as fatal reactivation of previously quiescent virus can occur)
- Postpone the injection or infusion if the patient has a cold sore, has had a cold in the past week, or has unexplained new symptoms that might be an infection
- Discontinue biologicals for four weeks before surgery. Patients should not start or restart the biologicals until after their sutures or staples are removed and there is no sign of infection
- Warn patients that a rash, burning sensation, or itch may develop at the injection site, which may last 10 to 14 days without leaving a scar

*The New York Heart Association’s functional classification system

**Fig 2 | Comparison of each biological drug with placebo for harm (withdrawals because of adverse events)**

### Withdrawals because of adverse events

<table>
<thead>
<tr>
<th>Biological</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>1.08 (0.62 to 1.87)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.02 (0.70 to 1.48)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1.65 (0.85 to 3.19)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>1.37 (0.81 to 2.34)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.28 (0.92 to 1.78)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>1.11 (0.63 to 1.95)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2.04 (1.43 to 2.91)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1.31 (0.78 to 2.21)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.38 (0.76 to 2.50)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.32 (1.06 to 1.64)</td>
</tr>
</tbody>
</table>

**P (drug)<0.0001**
and monitored.

Box 3 outlines in more detail how biologicals are taken and monitored.

### How are the new biologicals taken and monitored?
- Start treatment with methotrexate monotherapy or in combination with one or more other non-biological DMARDs (hydroxychloroquine, sulphasalazine, leflunomide) as soon as rheumatoid arthritis is diagnosed.
- Aim to reach a minimal target of remission or low disease activity with treatment; if the target is not reached, adjust treatment every one to three months and monitor strictly (measure C reactive protein and disease activity score or equivalent, as well as monitoring adverse events).
- If the treatment target is not achieved with the first DMARD strategy, consider adding a biological DMARD when poor prognostic factors are present (such as the presence of autoantibodies, a high disease activity state, or early erosive disease); in the absence of poor prognostic factors, consider switching to another DMARD strategy. In the UK, NICE guidance recommends using a biological if two trials of six months of traditional DMARD therapy have failed to control symptoms or prevent disease progression.
- When starting a biological, current practice would be to start with a tumour necrosis factor inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) combined with methotrexate.
- Patients with rheumatoid arthritis for whom a first tumour necrosis factor inhibitor has failed should receive a different biological.

#### TIPS FOR PATIENTS

### What is rheumatoid arthritis?
Rheumatoid arthritis causes your immune system to attack and inflame the lining of your joints. It often starts in the hands and feet: your joints become hot, swollen, stiff, and painful. Without treatment, inflammation permanently destroys the joints.

### How is it treated?
Early treatment with drugs such as methotrexate is important. If methotrexate (alone or in combination with other pills) is not controlling the inflammation, people are advised to take stronger, “biological” treatments as well such as etanercept (Enbrel). There are several different biological drugs, which all work by blocking cells and substances in the body that contribute to the inflammation.

### What is it like to take biologicals?
Some biologicals are given through a needle or tube inserted into your vein, in a clinic. Others are injected under the skin in different parts of your thigh or abdomen. A nurse or doctor teaches you how to do this. A family member or friend can also learn. You store the drug in a refrigerator and warm it to room temperature before use. Most people who fear self injection are able to give these injections with mild or no discomfort.

### What are the benefits and harms of taking a biological drug?
People who take a biological will have a better chance of a major improvement in pain, disability, and the number of tender and swollen joints than those who do not. People taking a biological are more likely to avoid serious joint damage. However, people who take a biological might get a rash, or burning, or itching at the injection site. This may last 10 to 14 days without leaving a scar. Rarely, a person may get tuberculosis from taking a biological. Before starting biologicals, a tuberculosis test is usually done. The drug is stopped if people develop a high fever or have an active infection and are taking an antibiotic.

### Is there anything else I should know?
- Before starting treatment, you must tell your doctor about all the medications that you are taking and whether you have had any allergic reactions.
- You should also let your doctor know if you have any infections, especially serious infections like tuberculosis. It is also important to tell your doctor if you have had cancer; are pregnant or breastfeeding; or are recovering from surgery or planning to have surgery.
- People with multiple sclerosis and people with severe congestive heart failure should not take biologicals.

### How cost effective are biologicals?
Biologicals are more expensive than traditional DMARDs. Two recent systematic reviews of studies of economic evaluations in rheumatoid arthritis found mixed results on the incremental cost effectiveness ratios. The systematic review for the European League Against Rheumatism’s guidelines found 25 published cost effectiveness studies, with costs ranging from $14 000 (£9000; €10 000) to over a million dollars per quality adjusted life year (QALY) gained. It concluded that if long term functional impairment and productivity losses are considered, then most estimates for the use of biologicals (in combination; after failure of traditional DMARDs; and others after failure of one tumour necrosis factor inhibitor) fall below the benchmark of $50 000 per QALY gained that many approval agencies use.

A similar systematic review over the same period but with slightly different criteria found 18 cost effectiveness analyses. Its more cautious conclusions were that at the threshold of $50 000 per QALY gained, biologicals were not cost effective in patients who failed methotrexate combination therapy or sequential administration of DMARDs. Evidence of cost effectiveness in patients who failed methotrexate monotherapy may have been limited by the choice of comparator, methotrexate-resistant patients who continued to receive methotrexate.

Both reviews agreed that the most cost effective approach for managing rheumatoid arthritis seems to be to treat with a DMARD early in the course of the disease, to move through a sequence of other DMARDs, and if non-response continues, to add a biological. Many assumptions had to be made in coming to these conclusions.
Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).


because of lack of prospective data on long term responses to biologicals; the fact that different quality of life weights yield different cost effectiveness ratios; lack of consensus on the appropriate way to measure quality of life weights; and the lack of an agreed approach to determine the potential of biologicals to reduce downstream costs. Cost effectiveness may improve if the price of biologicals falls with the emergence of biosimilars (follow-on biologicals) and increasing competition.

What might the future hold for the biologicals?

Different combinations of biologicals may achieve a more complete shutting down of the inflammation and joint damage; however, increased rates of infection have been seen with abatacept plus etanercept, and anakinra plus etanercept. Systemic inflammation is hypothesised to increase cardiovascular risk in patients with rheumatoid arthritis, and whether biologicals provide cardioprotection requires further study. We require long term data on benefits and safety of different biologicals. As few controlled trials can be continued ethically for more than one year, clinical epidemiologists and pharmacoepidemiologists need to agree on developing national and international registries that provide such data.22 23

Our case scenario

The patient was given information on the biologicals, and a decision aid that provided the evidence and trade-offs and elucidated her preferences (http://musculoskeletal.cochrane.org/decision-aid). She elected to continue the methotrexate and start weekly subcutaneous etanercept injections. Six months later, her symptoms and function had improved and she was enjoying walking the dog again. No new erosions were visible on radiography.

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Acute aortic dissection is caused by an aortic intimal tear with propagation of a false channel in the media. Depending on the site and extent of the tear, it may cause chest, back, or abdominal pain, or collapse caused by rupture or malperfusion (transient or persistent ischaemia of any organ as a result of arterial branch obstruction). It is anatomically categorised according to involvement of the ascending aorta (type A, DeBakey type I/II) (fig 1); the categorisation dictates management.

Why is aortic dissection missed?

Although most patients present within two hours of onset of symptoms (usually to non-cardiac surgical centres), definitive diagnosis may be delayed by over 12 hours and half of patients do not have surgery until more than 24 hours have elapsed. Patients with dissection are commonly hypertensive in their 60s, but all ages are affected (27% are aged 17-59 years, 40% aged 60-74 years, 33% aged >75 years), including young adults, some with connective tissue disorders, such as undiagnosed Marfan syndrome. In older patients, other conditions are more prevalent, and in the young, the diagnosis may not be considered.

The clinical features at presentation (table) may be sensitive but highly non-specific indicators and in some instances may include features of ischaemia from malperfusion (such as neurological deficits), which may confuse the clinical diagnosis. Electrocardiographic and troponin abnormalities resulting from coronary malperfusion are common and diagnostically misleading. Although changes in chest radiographs are common (89%), a normal chest radiograph does not exclude the diagnosis, and anteroposterior projections are unreliable. Guidelines for evaluating chest pain from the National Institute for Health and Clinical Excellence (NICE) concentrate on acute coronary syndrome (which is more common and less lethal). The need for chest radiographs, and their timing, is discretionary and inquiry for transient neurological deficits is not mandatory.

Why does this matter?

For type A acute aortic dissection, untreated mortality is 1-2% per hour in the first day, with a 90% mortality at 30 days. With surgery, this can be converted to 75-90% survival, and no more than two patients need treatment to gain survival advantage. Rapid recognition and treatment (within hours) may prevent the survival attrition and maximise recovery of reversible malperfusion phenomena (including neurological deficit). Misdiagnosis as acute coronary syndrome may lead to inappropriate administration of anti-platelet agents and thrombolysis, complicating surgery. For all cases of acute aortic dissection, delayed diagnosis may delay antihypertensive treatment, allowing propagation and worsening of prognosis.

CASE SCENARIO

A 64 year old hypertensive man presented to an emergency department with sudden onset, severe, sharp chest pain. Right arm blood pressure was 100/70 mm Hg and an electrocardiogram showed inferior ST segment depression. Troponin T was raised (0.2 ng/ml). Acute coronary syndrome was provisionally diagnosed, anti-platelet therapy administered, and coronary angiography planned. On later questioning, he described a left arm weakness that had resolved. Further examination noted left arm hypertension (155/90 mm Hg), a right carotid bruit, and diastolic murmur. Computed tomography showed a type A acute aortic dissection (see fig 2 for an example from another case) involving the right coronary ostium and brachiocephalic artery. He was transferred for emergency surgery.
How is acute aortic dissection diagnosed?

Clinical
A triad of symptoms—characteristic chest pain (usually abrupt and/or severe), a pulse deficit or blood pressure differential, and an abnormal chest radiograph—increases the likelihood of dissection but is present in only a third of patients. A pulse deficit is the unilateral absence or diminution of a pulse compared with contralateral palpation. To detect this, a full peripheral pulse examination is mandatory (radial, brachial, carotid, and femoral pulses). The blood pressure differential is defined as a difference in systolic blood pressure between both arms of >20 mm Hg.

Ask about any new neurological symptoms (transient or permanent) or symptoms of limb ischaemia, as these may highlight malperfusion phenomena and because focal neurological deficits occur in 17% of patients with type A dissection. In addition, for patients who are admitted with neurology or limb ischaemia, questioning about chest pain should be done to identify potential triggering causes of the presenting symptoms. The table outlines the key clinical features of both type A and B dissection.

Investigations
Patients with a suspected clinical diagnosis of acute aortic dissection should have basic investigations. These include electrocardiography, chest radiography, and blood tests for markers of myocardial ischaemia. Normality or abnormality of any of these does not exclude dissection; however, if further imaging rules out dissection, then they may be of use in future patient management. Once clinically suspected, a definitive diagnosis is made with cross sectional imaging (computed tomography of the aorta or magnetic resonance angiography) or transoesophageal echocardiography; each of these imaging techniques has high diagnostic accuracy. If computed tomography is done, images of the thoracic aorta should be obtained before injection of contrast to allow the detection of intramural haematoma (a condition that may progress to dissection). In the absence of trauma, computed tomography is not routine. Transthoracic echocardiography may be specific but is insensitive and operator dependent and does not exclude the diagnosis. Biomarkers may have a role: raised concentration of D-dimer is sensitive but non-specific, does not exclude the diagnosis. Biomarkers may have a role: raised concentration of D-dimer is sensitive but non-specific, does not exclude the diagnosis.

How is acute aortic dissection managed?
Administer analgesia for pain relief and control hypertension with intravenous β-blockade, and refer all patients to cardiac surgical centres: (a) in patients with type A dissection, for emergency surgery to prevent intrapericardial rupture, restore true luminal flow and aortic valve competence, and to correct malperfusion; (b) in patients with type B dissection, for medical management and assessment for complications, which may require surgical or endovascular intervention.
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5 Information Centre for Health Education and Social Care. Hospital episode statistics online. www.hesonline.nhs.uk.

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PICTURE QUIZ

Ankle injury after a fall from a horse

1 The radiographs of the right ankle show a total talar dislocation with a lateral malleolar fracture (figs 1 and 2).
2 The neurovascular status of the foot needs to be assessed and an emergency closed reduction attempted under general anaesthesia.
3 Post-procedure computed tomography should be performed to check for associated fractures and adequacy of joint reduction.
4 Avascular necrosis of the talus and post-traumatic subtalar osteoarthritis are complications associated with this injury.

STATISTICAL QUESTION

Survival (time to event) data: censored observations

Answers b and c describe a trial participant with a censored observation.

ON EXAMINATION QUESTION

Restless legs syndrome

Answer C is correct.

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