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Treatment of rheumatoid arthritis and other inflammatory disorders with biological drugs

Objectives:

- Be able to give examples of inflammatory disease, notably rheumatoid arthritis (RA).
- Know the principal symptoms of rheumatoid arthritis, disease progression and consequences for the patient.
- Be aware of the important biological and environmental factors associated with and possibly contributory to the pathogenesis of RA.
- Know the clinical criteria for the diagnosis of RA and current aims of treatment.
- Be able to outline the treatment of RA with biological drugs.
- Know why methotrexate is used in RA.
- Know how biological drugs are administered.
- Know some adverse effects of biological drugs.
- Be familiar with the mechanism of action and uses of some anti-inflammatory biological drugs:
  - abatercept
  - adalimumab
  - anakinra
  - etanercept
  - infliximab
  - rituximab.
Several inflammatory diseases, including some of autoimmune aetiology, are
either being treated with biological drugs or under clinical investigation with
these drugs. A list of some of these diseases is given below and representative
examples are dealt with in more detail:

- Alzheimer’s disease
- arthritis
- asthma
- atherosclerosis
- Crohn’s disease
- colitis
- dermatitis
- diverticulitis
- hepatitis
- irritable bowel syndrome (IBS)
- systemic lupus erythematosus (SLE)
- nephritis
- Parkinson’s disease
- psoriasis
- ulcerative colitis.

Traditionally, many of these have been treated with drugs such as analgesics
and corticosteroids for the symptoms of the disease. The advent of the bio-
logical remedies has now radically changed the approach to treatment, because
these drugs not only provide relief from pain, but block the important endogen-
ous mediators of inflammation, having analgesic and anti-inflammatory
actions, and also possibly significantly slow the chronic process of tissue
damage, thereby extending the useful life of the tissues, organs and joints.

**Rheumatoid arthritis**

The principal symptom of rheumatoid arthritis (RA) is inflammation of the
joints. Inflammation may also occur in other tissues, including, for example,
the heart, lungs, kidneys and pleura. The cause is currently unknown, but may
involve climate, working conditions and gender, because it is more prevalent
in women (F:M approximately 2.5 : 1.0). RA is diagnosed through its distinc-
tive effects on the joints and in skin, and the diagnosis is reinforced by the
presence in serum of the rheumatoid factor (RF), although its presence is not
mandatory for diagnosis of RA. RA is systemic in that it may attack several
different joints, and in many cases appears to affect different joints at different
times, hence the term ‘migratory or flitting polyarthritis’ used by some author-
ities. Over time, irreparable damage is done to the joint due to inflammation
of the synovial membrane, which forms the lining of the tendon sheaths and
the joints. As the disease progresses, it destroys the joint tissues and reduces
joint mobility through, for example, erosion and tethering of the tendons. This means that the tendon becomes fixed to adjacent tissues, which restricts its movement. Eventually, use of joints in the hands and limbs is lost, and fingers and toes may become severely deformed. In the skin, subcutaneous nodules form, and vasculitis may also be diagnosed, which is the chronic destruction of blood vessels. Several other haematological, radiological and biochemical tests are used to confirm the diagnosis but are not dealt with here. RA has traditionally been associated with morbidity and significantly earlier mortality.

**Important environmental and biological factors associated with or possibly contributory to the pathogenesis of RA**

- Cigarette smoking.
- Tumour necrosis factor (TNF)-α activity.
- Abnormal and inappropriate B-lymphocyte activity, i.e. abnormal antibody production.
- Detection of circulating autoantibodies against Ig Fc; these autoantibodies have been termed ‘rheumatoid factor’, and they may be involved in the inappropriate presentation of antigens to T cells by B cells.
- Abnormal activity of certain signalling pathways in synovial tissue, e.g. the Wnt signalling pathway, which is involved in embryonic development and cell renewal. In patients with RA, it has been reported that the synovial cells have abnormally high activity of the Wnt gene, as well as a number of other genes for several of the cytokines, cell adhesion molecules and chemokines. At present, it is not known whether these abnormalities are causative or a result of the more fundamental abnormalities.

**Diagnosis of rheumatoid arthritis – clinical criteria**

The criteria listed below are those published by the American College of Rheumatology in 1987. Any four of the criteria listed below must be identified for positive diagnosis of RA:

- detection of serum RF
- morning stiffness for 1 hour or longer for 6 weeks or more
- arthritis in three or more joints persisting for 6 weeks or more
- persistence for 6 weeks or more of symmetrical arthritis
- persistence for 6 weeks or more of arthritis of the hand joints
- rheumatoid nodules
- observation, using hand radiographs, of changes, erosion or unequivocal bony decalcification.
More recently, The Royal College of Physicians published guidelines for management and treatment of RA in adults, which take into account the patient’s history. In particular, these guidelines help to distinguish between RA and some other self-limiting inflammatory condition. For more information, the reader is referred to the publication by the Scottish Intercollegiate Guidelines Network Management of Early Rheumatoid Arthritis (see end of chapter).

**Current aims of treatment of RA**

- Slow the rate of disease progression.
- Control inflammation and pain; ideally the patients should be as free as possible from pain.
- Design the appropriate treatment regimen for each patient.
- Regular appointments with the clinic and the rheumatologist.
- Regular patient monitoring for adverse effects of treatments.
- Regular blood tests.
- Monitor patient compliance.

**Treatment of rheumatoid arthritis with biological drugs**

Traditionally, RA was treated symptomatically with non-steroidal and steroidal anti-inflammatory drugs, which still have a place in the management of RA. The use of these drugs is self-limiting through the corrosive effects of non-steroidal drugs such as aspirin on the gut and the serious effects of steroidal drugs on, for example, water retention and redistribution of body fat. Paracetamol is an alternative to aspirin for treatment of pain, but has a relatively low therapeutic index. Furthermore these treatments do not slow the progression of tissue damage and loss of hand use and mobility. Several drugs, e.g. methotrexate, penicillamine, gold and azathioprine, commonly known as DMARDs, or disease-modifying anti-rheumatic drugs, have been used for several years. These may provide symptomatic relief and slow the progression of the disease, but are associated with serious adverse effects and are relatively non-specific in their actions.

The biological DMARDs have been developed thanks to the advances made in molecular biology, and especially with regard to the identification of key cellular mediators of inflammation. Essentially, these are monoclonal antibodies (MAbs) directed against chemical mediators of inflammation, notably TNF-α, and interleukins IL-1 and IL-6. These MAbs compete with the endogenous ligands at their receptor sites on cells, e.g. CD20 and CD22, some of which have no identified endogenous ligand (at the time of writing).

The introduction of the biological drugs, also termed ‘biological DMARDs’, seems set to bring more benefit to patients in this respect but they
too may have serious adverse effects due to the lowering of resistance to infection through their powerful inhibition of the immune system.

The advantages associated with the use of the new biological DMARDs include:

- Restoration of joint function and reduction in joint stiffness, swelling and pain
- Production of significant periods of remission from symptoms
- Significant extension of usable joint life
- Significant reduction of early morning stiffness of joints
- Measurable reduction of the rate of joint damage
- Measurable reduction of levels of measurable markers of disease, e.g.
  - ESR (erythrocyte sedimentation rate)
  - C-reactive protein
- Reduction in measurable disease activity scores.

**Disadvantages**

- A most serious consideration for prescribers and public health organisations such as the NHS is their current cost, which should, however, be mitigated through the considerable savings from reduced patient care costs associated with progressive disablement and severity of disease symptoms. Furthermore, with time the costs of these drugs should fall significantly.
- MAbs suppress the immune response and may facilitate opportunistic infections, which necessitates the careful screening of potential recipients for the presence of any potentially dangerous pathological condition, e.g. respiratory infection
- MAbs are contraindicated in patients with moderate-to-severe heart failure, active tuberculosis, known hypersensitivity to murine (mouse)-derived products (several biological DMARDs have murine-derived macromolecular components)
- Adverse reactions during and after administration (see below).

**The use of methotrexate alone or together with biological DMARDs**

Methotrexate is prescribed alone as a DMARD for RA. It does take down tissue swelling and reduces pain, and will slow the rate of progression of joint damage and degeneration. It is prescribed together with the biological DMARDs in order to attenuate any immune reaction to the latter. The drug needs to be used with caution because it is a folic acid antagonist, and it is recommended that a dose of 5 mg folic acid be taken with each weekly dose of methotrexate (usually 7.5–20 mg weekly). Regular blood cell counts are strongly recommended for patients who take methotrexate.
**Administration of biological drugs**

Many of the biological drugs, e.g. infliximab and rituximab, are administered by intravenous infusion and are therefore given under clinical supervision in hospital. A nurse, doctor or other carer, on the other hand, may administer etanercept to the patient in hospital or at home.

**Intravenous infusion methods**

*Adverse effects of biological drugs*

Adverse effects may be considered in terms of infusion-related reactions and post-infusion reactions, e.g. with infliximab, infusion-related adverse effects notably include dyspnoea, headache and urticaria. These effects cannot with certainty be attributed to the drug or the physical process of perfusion because, in at least one study, up to 40 of patients suffered adverse reactions to infusion of a placebo. Post-infusion adverse reactions with infused or injected TNF-α inhibitors include optic neuritis, central nervous system (CNS) demyelination and opportunistic malignancies, e.g. lymphomas. Adverse neurological reactions reported include seizures and the reader is advised to refer to the most up-to-date published data available for each biological drug. There is little doubt, however, that the introduction of the biological drugs, especially in the treatment of diseases such as RA, Crohn’s disease and cancer (see Chapter 7), has vastly improved the quality and duration of life for many millions of sufferers of rheumatic diseases and cancer (see Chapter 7).

In principle, the biological treatments act in a manner similar to that of many of the more conventional drugs in that they are receptor-blocking drugs, which are designed to bind to specific cell surface receptors on, for example, T or B cells, thereby preventing the endogenous inflammatory agents from triggering the immune response. Examples are shown in Figure 6.1, and these are described in more detail here.

**Abatacept**

Abatacept (Orencia) is a soluble fusion protein, prepared by fusing the extracellular domain of the human cytotoxic T-lymphocyte-associated antigen (hCTLA-4) to a modified human G1 immunoglobulin. When abatacept binds to its target receptors, namely CD80 and CD86 on the T cell, it prevents endogenous ligands from binding and blocks the inflammatory cascade. Normally, two processes activate T cells, namely the binding of the T-cell receptor to the antigen–MHC complex on the antigen-presenting cell (APC) and the binding of the T cell’s CD28 receptor to receptor proteins on the surface of the APC. Abatacept binds to the B7 protein receptor with high affinity and thus blocks binding of B7 protein, thereby blocking the
inflammatory reaction. The site of action of abatacept on T cells gives it more scope as an immunosuppressant than others that act further down the inflammatory cascade, e.g. on the B cells.

Abatacept is prescribed together with methotrexate, another DMARD. This is because abatacept, as with the other biological DMARDs, is a foreign protein and may elicit an immune response by the host immune system. Methotrexate is a relatively small molecule that limits the immune response, thus sparing the foreign protein so that it can attenuate the host immune system’s response.

**Adalimumab**

Adalimumab (Humira) is a completely human MAb that exhibits high affinity and specificity for TNF-α, blocking binding to its receptors. Adalimumab is supplied as a prefilled syringe containing 40 mg adalimumab, or as an auto-injector system and self-administered as a subcutaneous injection every other week. In some patients who do not respond satisfactorily to this dose it has been prescribed for once-weekly injection. It has been prescribed either alone

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**Figure 6.1** Mechanisms of action of some biological drugs. (After Cohen M. Abatacept in focus. *Internet J Rheumatol* 2007;3(1).)
or with methotrexate. It has been found to be effective not only for RA but also for Crohn’s disease, (see below), ankylosing spondylitis and psoriatic arthritis. Patients usually feel the benefits about 1–4 weeks after starting treatment.

The adverse effects of adalimumab, as for many other biological drugs that block TNF-α, include susceptibility to opportunistic infections, including upper respiratory tract and urinary tract infections. Blood tests have revealed antinuclear antibodies (ANAs) in some patients with symptoms of SLE. Patients with latent TB may suffer reactivation during or after a course of adalimumab or with other biological DMARDs. Skin rashes, mouth ulcers and gastrointestinal disorders have been reported. Readers are referred to the BNF for more details of adverse reactions.

Anakinra
Anakinra (Kineret) is a recombinant antagonist at the IL-1 receptor. Chemically it is based on the structure of the IL-1RA receptor. It blocks the inflammatory actions of IL-1 by binding to it, thus blocking the cartilage degradation and inflammation caused by IL-1. In the UK anakinra is currently not recommended for the treatment of RA except as part of a clinical trial.

Etanercept
Etanercept (Enbrel) consists of a fully human amino acid sequence p75 TNFR1 dimer linked to the Fc of human IgG. It acts by blocking the binding of TNF-α to its receptor. It was the first biological approved by the US Food and Drug Administration (FDA) for the treatment of psoriatic arthritis. It is a dimer that can bind to two TNF-α receptors, whether free or cell bound, with very high affinity. As with several other MAb treatments, etanercept is often prescribed together with methotrexate. Through its widespread use, much is known of the clinical efficacy, safety and adverse effects of etanercept. The most frequently noticed adverse effect is a mild-to-moderate injection site reaction, which generally disappears with multiple use. The most serious adverse reactions, including fatalities, occur when the drug is used in patients who are also on immunosuppressant drugs, who are immunocompromised or who have existing infections such as sepsis.

Infliximab
Infliximab (Remicade) was the first biological anti-rheumatic treatment successfully developed for clinical use. It is a monoclonal antibody made up of a chimaeric human Hgl–murine Fv1 gene complex, which binds both membrane-bound and soluble TNF-α with strong affinity. After infliximab administration, there are significant falls in the blood concentrations of some cytokines, notably IL1-RA (an IL-1 receptor antagonist), and of soluble TNF-α receptors, both of which contribute to the inflammatory response. These effects correlate well with the reduction in the symptoms of
inflammation. Infliximab may also reduce the angiogenesis associated with the inflammatory response. Infliximab is still heavily prescribed in view of its high efficiency.

**Rituximab**
Rituximab (MabThera), together with methotrexate, is approved for the treatment of neoplastic diseases, e.g. follicular lymphoma (see page 70), and is also prescribed for RA in patients with active and severe RA that is refractory to other anti-rheumatic treatments. Rituximab was genetically engineered as a mouse/human chimaeric monoclonal IgG1 k antibody directed against the CD20 receptor. It consists of variable light and heavy chain murine antibody sequences linked to constant human sequences. CD20 occurs as a transmembrane receptor on the surface of B cells and rituximab binds to it with very high affinity (molar dissociation constant about 7.5–10 nmol/L). Rituximab is administered by slow intravenous infusion.

The B cell clearly is a significant player in the aetiology of RA. In RA, the synovial cell B cells may secrete significant amounts of inflammatory cytokines including TNF-α. Furthermore, B cells may also function as APCs, which display the foreign antigen complex with the MHC on its surface. T cells may then recognise this complex through their T-cell receptor.

### Clinical scenario – rheumatoid arthritis

A 14-year-old girl had presented initially at the age of 8 with painful flitting polyarthritis affecting mainly the hips, ankles, fingers and wrists. Radiographs revealed erosion in the ankles and hips, and throughout the history of her disease she had needed occasional use of a wheelchair. During flares she had been prescribed intra-articular steroid injections and infusions of methylprednisolone to extend remission periods. She was prescribed methotrexate at a dose of 17.5 mg once weekly and over the next 2 years was prescribed several different biological drugs, namely adalimumab, etanercept and infliximab. Eventually rituximab (1 g – a humanised anti-CD20 MAb) was prescribed by intravenous infusion with a repeated infusion of this dose after 2 weeks. Parameter changes: the Child Health Assessment Questionnaire (CHAQ) score dropped from 1.6 before treatment to 0.3 after treatment. Active joint counts were reduced from 6 to 0.

### Psoriasis

Psoriasis is a chronic inflammatory disease that targets principally the skin and one that is possibly of autoimmune aetiology. Skin in many patients
becomes reddened and scaly (psoriatic plaques) due to inflammatory reactions and excessive production of skin in these localised areas. There is no general pattern to the distribution of plaques and several forms have been identified. Plaques may occur, among other regions, on the legs and arms, at the joints, on the genital organs or on the scalp. These are the most prevalent forms and are termed ‘psoriasis vulgaris’ or ‘plaque psoriasis’. In some patients inflammation is confined to finger- and toenails, when the term ‘psoriatic nail dystrophy’ is used. A form of arthritis (psoriatic arthritis) is diagnosed when the inflammation occurs at the joints. Other forms of psoriasis include flexural psoriasis, which manifests itself in the folds of the skin, e.g. under the arms or on genital folds. The most severe and potentially fatal form is erythrodermic psoriasis, when most of the skin peels off with consequent loss of temperature regulation and the loss of barriers to the external environment. In addition to physical stress, many patients with this (and other disfiguring skin conditions) become acutely self-conscious and may even become reclusive.

The cause or causes of psoriasis are unknown with certainty, and theories are based on the degree of success of different treatments, e.g. the success of immunosuppressants in temporarily clearing plaques lends weight to the idea that psoriasis may be an autoimmune disease. Alternatively, the lesion may be confined to the skin itself, in which there is abnormal and unregulated overproduction of skin in certain areas of the body. Dry as opposed to oily skin appears more vulnerable. Stress, infection or seasonal factors may contribute. Putative chemical irritants include alcohol, cigarette smoking and drugs, e.g. β blockers and chloroquine, an antimalarial drug. Precipitation of the disease has been reported following, for example, antimalarial drugs, antibiotics such as streptomycin, β blockers and lithium salts.

The genetic aetiology of psoriasis (and of course those of several other inflammatory diseases) is currently the subject of much research because this knowledge provides direction for the design of biological drugs. In the case of psoriasis, linkage analysis, which attempts to establish links between different genes in families in order to study disease-producing mutations, has produced evidence for at least nine loci on different chromosomes that are linked to the occurrence of psoriasis. The genes identified are called psoriasis susceptibility genes 1–9 (PSORS1–9). Several of these mutated genes have been implicated in the occurrence of psoriasis. An interesting finding is that gene PSORS1, on chromosome 9, which is the most commonly occurring linkage gene, controls the production of certain proteins that occur in abnormally high amounts in the skin of people with psoriasis, and also the production of components of the immune system. Of particular interest are genes that direct the upregulation of TNF-α and interferon-α.
Treatment of psoriasis

Traditional treatment may be topical, when soothing and emollient creams, lotions and ointments are applied directly to affected areas. Drugs used are relatively traditional preparations, including coal tar and mineral oil, and topical corticosteroids. These are of limited value, and corticosteroids are associated with skin thinning and rebound flares when withdrawn from use. Traditional systemic treatments include corticosteroids, which have severe adverse effects with prolonged use. Other immunosuppressants used include anti-metabolites and cytotoxic drugs, e.g. methotrexate, azathioprine and ciclosporin.

Treatment of psoriasis with biological drugs

The biological drugs used target specific inflammatory mediators or cells (see above). Drugs used include adalimumab, etanercept, infliximab and ustekinumab, which binds to IL-12 and IL-23 and blocks their action.

Systemic lupus erythematosus

SLE (lupus) is an autoimmune inflammatory disease that attacks mainly the connective tissues of the body. It may be localised to specific areas, organs and tissues, or be widespread. Tissues and organs commonly attacked include the heart, lungs, blood, skin, kidneys, liver and the nervous system. The disease is generally characterised by intermittent flare-ups and periods of remission. Gender plays an important part because the ratio of occurrence in women:men is about 9 : 1 and is more prevalent in non-European populations. Currently there is no known cure and SLE is treated symptomatically and in an attempt to blunt the immune system.

Aetiology of SLE

The cause or causes of SLE are unknown. Symptoms vary with the parts of the body affected. The common symptom is inflammation. It is not always easy to diagnose when symptoms first present themselves and may easily be misdiagnosed, e.g. a patient, perhaps a teenage girl, may soon after the onset of menstrual cycles start to exhibit aberrant and violent emotional behaviour, which may be dismissed as a sign of adolescence and if left untreated may result in a full-blown psychosis. This results from inflammation of the meninges or neuronal blood vessels. In other patients, the symptoms may include fatigue, joint pain and malaise.

A fairly definitive symptom is the malar or butterfly rash on the face. The skin is particularly susceptible, and patients may present with inflamed,
scaly patches on the skin, referred to as discoid lupus. Mucous membranes are susceptible to the inflammatory reaction. Patients complain of ulcers of the vagina, mouth or nose. Alopecia (hair loss) may occur. More seriously, there may be inflammation of pulmonary tissues resulting in, for example, shrinking lung syndrome, pulmonary hypertension and pulmonary emboli.

Perhaps the most serious manifestation of lupus is in the kidneys, when the patient presents with painless proteinuria or haematuria. If left untreated this may result in acute or end-stage renal failure.

**Crohn’s disease**

Crohn’s disease is named after the American gastroenterologist Burril Bernard Crohn, although the diagnosis of inflammatory bowel disorders is historically well documented and the disease may be named according to the region of the bowel affected e.g. Crohn’s ileitis, which is confined to the ileum, and the more prevalent type, which attacks mainly the large intestine. Crohn’s disease affects both the ileum and the large intestine. Symptoms include fever and weight loss in adults and growth retardation in children. There may also be other symptoms, e.g. inflammation of other tissues including the skin and eyes. The disease predisposes some patients to the possibility of malignant growths in the areas affected. The causes of the disease are not known with certainty, but probably involve both environmental and genetic inputs. In contrast to the role of hyperimmune activity in, for example, SLE and RA, Crohn’s disease appears to result from innate immune deficiency, possibly caused by a failure of macrophages to secrete certain protective cytokines. This exposes the patient to infection by opportunistic microorganisms. Patients generally experience periodic remission and relapse, and the aim of treatment is to sustain the periods of remission and prevent or diminish the damaging impact of relapse.

Diagnosis is confirmed using endoscopy, radiology and biopsy investigation.

Treatment is currently aimed at the treatment of symptoms when they occur and the establishment and maintenance of remission. Traditionally, glucocorticoids (corticosteroids) and 5-aminosalicylic acids have been used to treat inflammation and pain during relapse, and also immunosuppressant drugs such as methotrexate and azathioprine. More recently, newer biological drugs that inhibit the action of TNF-α, e.g. adalimumab and infliximab, are being used and these have proven, in many patients, to be very effective for inducing and maintaining remission.

More recently, it has been reported that naltrexone may be useful for induction and maintenance of remission.
The impact of treatment costs on treatment of RA (and other autoimmune problems) with biological drugs

The prevalence of RA is such that there is relatively heavy prescribing of the biological drugs, which at present are expensive when compared with the older treatments, e.g. a vial of infliximab (Remicade) was priced in the September 2009 issue of the BNF (British National Formulary) at £419.62 for a vial containing 100 mg. Assuming a patient weight of 65 kg, and given that the recommended dose is 3 mg/kg, the patient would be given 195 mg from two vials at a cost of £839.24. After 2 and 6 weeks the same doses are given, incurring a further cost of £1678.48, followed by similar doses every 8 weeks, which adds a further six treatments costing £5034.44. The total cost over 12 months is therefore £7552.16. In terms of patient relief from pain, improved quality of life and the slowing of the degenerative process, the cost becomes irrelevant. Furthermore, if previous experience is anything to go by, the cost of these treatments is likely to fall, particularly when generic alternatives become available.

Multiple choice questions

For each question, a maximum of five options is provided and only one is correct.

1 Factors possibly contributory to RA pathogenesis include:
   a Abnormally high TNF-α activity
   b Deficient antibody production
   c Mutations of rheumatoid factor
   d Abnormally low expression of the Wnt gene
   e Persistent hyperthermia

2 The clinical criteria for diagnosis of RA include:
   a Rheumatoid nodules
   b Absence of rheumatoid factor
   c Persistence for 7 days or more of morning stiffness for 1 hour or longer
   d Persistence for 2 weeks or more of arthritis in three or more joints
   e Raised white cell count

3 Current aims of treatment of rheumatoid arthritis:
   a Control of pain using sustained-release salicylate therapy
   b Three-weekly appointments with the district nurse
   c Slow the rate of disease progression
   d Regular counselling
The use of drugs to treat RA:

a. Salicylates no longer have a place in the management of RA
b. Paracetamol is not an alternative to aspirin for the treatment of pain
c. DMARD is the acronym for dental management with arthritis and other rheumatoid diseases
d. Biological drugs, including TNF-α antagonists, are now prescribed for the treatment of RA
e. MAbs have no place in the treatment of RA

Rituximab is an antineoplastic MAb, which:

a. Is not approved for the treatment of RA
b. Is directed against the CD18 receptor
c. Is a mouse/human chimaeric monoclonal IgG1 κ antibody
d. Is unavailable in the UK
e. Is administered by subcutaneous injection

Reference

Further reading
Cohen M. Abatacept in focus. *Internet J Rheumatol* 2007; 3(1).
Merck. Rheumatoid arthritis. *The Merck Manuals Online Medical Library*. Available at www.merck.com