festations are severe, but will eventually be needed in about 80% of cases.[2] DMARDs (generally methotrexate) are introduced when corticosteroid therapy fails to control the disease or when their adverse effects become problematic. Most patients will respond to methotrexate although liver function must be closely monitored. The value of other DMARDs is uncertain. Intravenous immunoglobulin is also frequently tried, although supporting evidence is lacking.[2,3]

The TNF-α inhibitors have also been tried,[2,3] but results have been variable.[2] There is, however, some evidence that interleukin-1 and interleukin-6 play a role in pathogenesis of the condition, and there have been a few reports of dramatic improvement with anakinra (an interleukin-1 receptor antagonist) in resistant disease, while tocilizumab (an interleukin-6 receptor antagonist) has also been suggested as an investigational therapy.[2,3]

The name Still's disease has also been used rather inconsistently to describe some types of juvenile idiopathic arthritis (above).

1. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. *Semin Arthritis Rheum* 2006; **36:** 144–52.
2. Pouchot J. How can we improve the management of adult-onset Still's disease? *Joint Bone Spine* 2007; **74:** 117–19.
3. Kontzias A, Efthimiou P. Adult-onset Still's disease : pathogenesis, clinical manifestations and therapeutic advances. *Drugs* 2008; **68:** 319–337.

Abatacept *(BAN, USAN, rINN)*

Abataceptum; BMS-188667; CTLA4-Ig. 1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment), bimolecular (146→146′)-disulfide.

Абатацепт

CAS — 332348-12-6.
ATC — L04AA24.
ATC Vet — QL04AA24.

Adverse Effects and Precautions

Acute infusion reactions occurring within 1 hour of starting an infusion are common with abatacept use. The most frequently reported infusion events are dizziness, headache, and hypertension; hypotension and dyspnoea occur less commonly. Other acute events include nausea, flushing, pruritus, rash, and wheezing. Most events are usually mild to moderate although stopping treatment may be necessary in a few patients.

Other common adverse effects include headache, nasopharyngitis, nausea, dyspepsia, diarrhoea, dizziness, back pain, fatigue, cough, and abnormal liver function values. Antibodies to abatacept may develop and anaphylaxis or anaphylactic reactions have been reported rarely. Uncommon adverse reactions include paraesthesia, thrombocytopenia, and leucopenia.

Infections are frequent in patients treated with abatacept and most often affect the respiratory and urinary tracts. More serious infections such as pneumonia, sepsis, cellulitis, bronchitis, diverticulitis, and acute pyelonephritis have also been rarely associated with abatacept treatment. Treatment should be stopped in patients who develop a serious infection. Abatacept should not be given to patients with severe and uncontrolled infections such as sepsis and opportunistic infections. It should be used with caution in patients with a history of recurrent infections, with underlying conditions that may predispose to infections, or with chronic, latent, or localised infections. Patients should be screened for latent tuberculosis before starting treatment; those testing positive should be treated with standard chemoprophylaxis before beginning abatacept.

Some disease-modifying antirheumatic drugs have been associated with hepatitis B reactivation; licensed product information for abatacept recommends screening for viral hepatitis before starting treatment.

Adverse effects of abatacept are more frequent in patients with chronic obstructive pulmonary disease and may include a worsening of their respiratory symptoms.

Carcinogenicity. The role of abatacept in the onset of malignancies such as lymphoma in humans is not known.

In placebo-controlled studies the overall frequency of malignancies in patients treated with abatacept compared to those that received placebo was similar (1.4% and 1.1%, respectively). However, there were more cases of lung cancer and lymphomas in those given abatacept. In *animal* studies in mice, increases in lymphomas and mammary tumours have been noted, although these increases have not been seen in some studies with other mammals.

Interactions

Live vaccines should not be given with abatacept, or within 3 months of stopping it, as its effect on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with abatacept may increase the risk of serious infections (see p.71); such combinations are not recommended. Use with anakinra or rituximab is also not recommended because of insufficient evidence to assess safety.

Pharmacokinetics

Abatacept is reported to have linear pharmacokinetics at usual dosages. After repeated intravenous doses, its mean terminal half-life is about 13 days.

Studies in *animals* suggest that abatacept is distributed into breast milk.

Uses and Administration

Abatacept, a fusion protein, is a co-stimulation blocker. It prevents the activation of T-cells; activated T-cells have been found in the synovium of patients with rheumatoid arthritis. It is used in the treatment of moderate to severe active rheumatoid arthritis to delay structural damage and improve physical function. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor; in the USA, it may be used to reduce the signs and symptoms of early disease.

Abatacept is given by intravenous infusion over a period of 30 minutes in the following doses, based on body-weight:

- 500 mg for patients weighing less than 60 kg
- 750 mg for those weighing 60 to 100 kg
- 1 g for those over 100 kg.

The dose is repeated at 2 and 4 weeks, then every 4 weeks thereafter. If a response to treatment is not seen within 6 months, the benefits of continuing abatacept may need to be considered. In the UK, abatacept is licensed for use with methotrexate; however, in the USA it may be given alone or with other DMARDs (but see Interactions, above).

For the use of abatacept in children, and recommended doses, see below.

Abatacept is also being studied for other auto-immune diseases such as inflammatory bowel disease, psoriatic arthritis, and SLE.

Administration in children. In the USA, abatacept is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 6 years and above; it may be used alone or with methotrexate. The dose is calculated according to body-weight and is given as an intravenous infusion over 30 minutes; those weighing less than 75 kg should be given 10 mg/kg initially, while heavier children may receive the appropriate adult dose (see above). Doses should be repeated at 2 and 4 weeks, and then every 4 weeks thereafter.

Rheumatoid arthritis. References to the use of abatacept in rheumatoid arthritis (p.11).

1. Kremer JM, *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003; **349:** 1907–15.
2. Genovese MC, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N Engl J Med* 2005; **353:** 1114–23. Correction. *ibid.*; 2311.
3. Kremer JM, *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; **144:** 865–76.
4. Weinblatt M, *et al.* Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006; **54:** 2807–16.
5. Nogid A, Pham DQ. Role of abatacept in the management of rheumatoid arthritis. *Clin Ther* 2006; **28:** 1764–78.
6. Pollard LC. Inhibiting costimulatory activation of T cells: a viable treatment option for rheumatoid arthritis? *Drugs* 2007; **67:** 1–9.
7. Lundquist L. Abatacept: a novel therapy approved for the treatment of patients with rheumatoid arthritis. *Adv Therapy* 2007; **24:** 333–45.
8. Russell AS, *et al.* Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007; **66:** 189–94.
9. Bruce SP, Boyce EG. Update on abatacept: a selective costimulation modulator for rheumatoid arthritis. *Ann Pharmacother* 2007; **41:** 1153–62.

Preparations

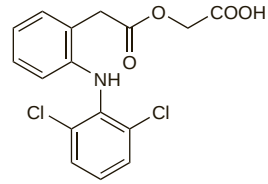
Proprietary Preparations (details are given in Part 3)
Arg.: Orencia; ***Cz.:*** Orencia; ***Fr.:*** Orencia; ***Port.:*** Orencia; ***UK:*** Orencia; ***USA:*** Orencia.

Aceclofenac *(BAN, rINN)*

Acéclofénac; Aceclofenaco; Aceclofenacum; Aceklofenák; Aceklofenak; Aceklofenakas; Aseklofenaakki; Aseklofenak. [*o*-(2,6-Dichloroanilino)phenyl]acetate glycolic acid ester; 2-(2,6-Dichloroanalino)phenylacetoxyacetic acid.

Ацеклофенак

$C_{16}H_{13}Cl_2NO_4$ = 354.2.
CAS — 89796-99-6.
ATC — M01AB16; M02AA25.
ATC Vet — QM01AB16; QM02AA25.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Aceclofenac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Hypersensitivity. Leukocytoclastic vasculitis, a type III hypersensitivity reaction, has been reported after therapy with aceclofenac.[1,2] Anaphylaxis has also occurred.[3]

1. Epelde F, Boada L. Leukocytoclastic vasculitis and hemoptysis after treatment with aceclofenac. *Ann Pharmacother* 1995; **29:** 1168.
2. Morros R, *et al.* Hypersensitivity vasculitis related to aceclofenac. *Br J Rheumatol* 1997; **36:** 503–4.
3. Rojas-Hijazo B, *et al.* Anaphylactic reaction after aceclofenac intake. *Allergy* 2006; **61:** 511.

Precautions

As for NSAIDs in general, p.98.

Aceclofenac should be avoided in patients with moderate to severe renal impairment.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Aceclofenac is well absorbed from the gastrointestinal tract; peak plasma concentrations are reached 1 to 3 hours after an oral dose. Aceclofenac is more than 99% bound to plasma proteins. The plasma-elimination half-life is about 4 hours. About two-thirds of a dose is excreted in the urine, mainly as hydroxymetabolites. A small amount is converted to diclofenac.

◊ It has been suggested[1] that low concentrations of diclofenac, a minor metabolite, may account for some of the actions of aceclofenac.

1. Hinz B, *et al.* Aceclofenac spares cyclooxygenase 1 as a result of limited but sustained biotransformation to diclofenac. *Clin Pharmacol Ther* 2003; **74:** 222–35.

Uses and Administration

Aceclofenac, a phenylacetic acid derivative, is an NSAID (see p.99) related to diclofenac (p.44). It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, in usual oral doses of 100 mg twice daily. Reduced doses should be used in patients with hepatic impairment, see below.

◊ Reviews.

1. Dooley M, *et al.* Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. *Drugs* 2001; **61:** 1351–78.
2. Reginster JY, *et al.* Comment positionner l'acéclofénac au sein de l'arsenal thérapeutique des pathologies ostéo-articulaires chroniques? *Rev Med Liege* 2001; **56:** 484–8.
3. Legrand E. Aceclofenac in the management of inflammatory pain. *Expert Opin Pharmacother* 2004; **5:** 1347–57.
4. Lee J, *et al.* Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch Pharm Res* 2005; **28:** 1097–1102.

Administration in hepatic impairment. The initial oral dose of aceclofenac should be reduced to 100 mg daily in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Berlofen; Bristaflam†; ***Austria:*** Beofenac†; ***Belg.:*** Air-Tal; Biofenac; ***Braz.:*** Aceflan†; Cecoflan†; Proflam; ***Chile:*** Airtal†; Bristaflam†; ***Denm.:*** Barcan; ***Fin.:*** Barcan; ***Fr.:*** Cartrex; ***Ger.:*** Beofenac; ***Gr.:*** Aceclonac; Arlina; Biofenac; Sovipan; ***Hung.:*** Aflamin; ***India:*** Aceclo; Arrestin; Movon; Zerodol; ***Ital.:*** Airtal; Gladio; Kafenac; ***Mex.:*** Bristaflam; ***Neth.:*** Biofenac; ***Norw.:*** Barcan; ***Philipp.:*** Clanza; ***Port.:*** Airtal; Biofenac; ***Rus.:*** Airtal (Аэртал); ***Spain:*** Airtal; Airtal Difucrem; Falcol; Gerbin; Sanein; ***Swed.:*** Barcan; ***Switz.:*** Locomin†; ***UAE:*** Aceclofar; ***UK:*** Preservex; ***Venez.:*** Airtal†; Bristaflam.

Multi-ingredient: ***India:*** Kinectine; Kinectine P; Kinectine-MR; Movon-MR; Movon-P†; Zerodol-MR; Zerodol-P.

Acemetacin *(BAN, rINN)*

Acemetacina; Acémétacine; Acemetacinum; Asemetasin; Bay-f-4975; Indometasinin Glikolik Asit Esteri; TVX-1322. *O*-[(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-yl)acetyl]glycolic acid.

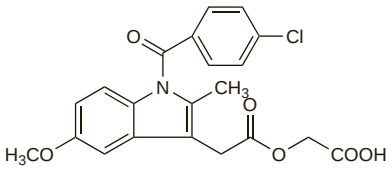
Ацеметацин

$C_{21}H_{18}ClNO_6$ = 415.8.

CAS — 53164-05-9.

ATC — M01AB11.

ATC Vet — QM01AB11.



Pharmacopoeias. In *Eur.* (see p.vii)

Ph. Eur. 6.2 (Acemetacin). A yellow or greenish-yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous alcohol; soluble in acetone. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Acemetacin is well absorbed after oral dosage. Its major metabolite is indometacin (p.66) which, after repeated doses, is present at higher concentrations than those of acemetacin. Acemetacin is bound to plasma proteins to a slightly lesser extent than indometacin. It is eliminated via both the liver and the kidneys.

Uses and Administration

Acemetacin, a glycolic acid ester of indometacin, is an NSAID (p.99). Its pharmacological activity is due to both acemetacin and its major metabolite, indometacin (p.66). Acemetacin is used in rheumatoid arthritis, osteoarthritis, and low back pain, and for postoperative pain and inflammation. Usual oral doses are 120 to 180 mg daily in divided doses. Acemetacin is eliminated by both hepatic and renal routes, although pharmacokinetics are not affected by moderate renal or hepatic impairment and appear to be unchanged in the elderly.

◊ References.

1. Jones RW, *et al*. Comparative pharmacokinetics of acemetacin in young subjects and elderly patients. *Br J Clin Pharmacol* 1991; **31:** 543–5.
2. Hazleman B, Bernstein RM. Acemetacin in the long-term therapy of rheumatoid arthritis. *Curr Med Res Opin* 1993; **13:** 119–26.
3. Chou CT, Tsai YY. A double-blind, randomized, controlled parallel group study evaluating the efficacy and safety of acemetacin for the management of osteoarthritis. *Int J Clin Pharmacol Res* 2002; **22:** 1–6.
4. Leeb BF, *et al*. Behandlung der Gonarthrose: Wirksamkeit und Verträglichkeit von retardiertem Acemetacin im Vergleich zu Celecoxib. *Orthopade* 2004; **33:** 1032–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Rheutrop; ***Cz.:*** Rantudil; ***Ger.:*** Acemetadoc; Acephlogont†; Rantudil; ***Gr.:*** Gamespir†; Rantutal; ***Hung.:*** Rantudil; ***Ital.:*** Acemix; Solart†; ***Jpn:*** Rantudil; ***Mex.:*** Rantudil; ***Philipp.:*** Rantudil; ***Pol.:*** Rantudil; ***Port.:*** Rantudil; ***Spain:*** Espledol; Oldan; ***Switz.:*** Tilur; ***Turk.:*** Rantudil; ***UK:*** Emflex; ***Venez.:*** Mostanol†; Pranex.

Multi-ingredient: ***Arg.:*** Rucaten Forte; Rucaten Prednisolona.

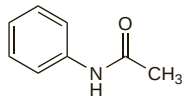
Acetanilide

Acetanilida; Antifebrin. *N*-Phenylacetamide.

Антифебрин; Ацетанилид

C_8H_9NO = 135.2.

CAS — 103-84-4.



Pharmacopoeias. In *Fr.*

Profile

Acetanilide, a para-aminophenol derivative related to paracetamol (p.108), has analgesic and antipyretic properties. It was replaced by safer analgesics.

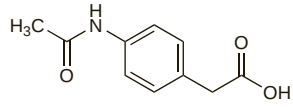
Actarit *(rINN)*

Actaritum; MS-932. (*p*-Acetamidophenyl)acetic acid.

Актарит

$C_{10}H_{11}NO_3$ = 193.2.

CAS — 18699-02-0.



Profile

Actarit is reported to be a disease-modifying antirheumatic drug. It has been given in the treatment of rheumatoid arthritis in a usual oral dose of 100 mg three times daily.

Adverse effects. A photosensitivity reaction developed in a 52-year-old woman one month after starting actarit and doxycycline.[1] Photopatch tests for both drugs were only positive for the patches containing actarit.

1. Kawada A, *et al*. Photosensitivity due to actarit. *Contact Dermatitis* 1997; **36:** 175–6.

Use. References.

1. Nakamura H, *et al*. Clinical effects of actarit in rheumatoid arthritis: improvement of early disease activity mediated by reduction of serum concentrations of nitric oxide. *Clin Exp Rheumatol* 2000; **18:** 445–50.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Mover†; Orcl.

Adalimumab *(BAN, USAN, rINN)*

Adalimumabum; D2E7; LU-200134. Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer.

Адалимумаб

CAS — 331731-18-1.

ATC — L04AB04.

ATC Vet — QL04AB04.

Adverse Effects and Precautions

As for Infliximab, p.69.

Injection site reactions including erythema, itching, pain, and swelling are the most common adverse reactions with adalimumab; however, most reactions are mild and do not result in drug withdrawal. Other common reactions include headache, rashes, back pain, hypertension, paraesthesias, increased alkaline phosphate levels, and cough.

Autoantibodies to adalimumab have been detected.

Interactions

As for Infliximab, p.71.

Methotrexate is reported to reduce the clearance of adalimumab by up to 44% but licensed product information for the latter states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Adalimumab is reported to have linear pharmacokinetics at usual dosages. After subcutaneous injection peak concentrations are reached in about 3 to 8 days and bioavailability is estimated to be 64%. The mean terminal half-life is about 2 weeks.

◊ References.

1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; **74** (suppl): 13–18.

Uses and Administration

Adalimumab is a recombinant human monoclonal tumour necrosis factor (TNF) antibody that binds specifically to TNF-α and blocks its interaction with endogenous cell-surface TNF receptors. It also modulates biological responses that are induced or regulated by TNF. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and Crohn's disease.

Adalimumab is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active and progressive **psoriatic arthritis** to delay structural damage and improve physical function. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs), although in severe progressive rheumatoid arthritis it may be used in patients not previously treated with methotrexate; in the USA, it may be used to reduce the signs and symptoms of early disease. Adalimumab is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used to reduce signs and symptoms in early disease. For all the above indications, it is given by subcutaneous injection in a dose of 40 mg every other week. In the treatment of rheumatoid arthritis, UK licensed product information recommends that adalimumab should be given with methotrexate, although monotherapy may be used where treatment with methotrexate would be inappropriate. When used as monotherapy in rheumatoid arthritis, some patients may benefit from increasing the dose to 40 mg every week. Clinical response is usually achieved within 12 weeks of treatment.

Adalimumab is also used in the treatment of moderate to severe, active **Crohn's disease** unresponsive to conventional treatment; it may also be used in patients who have relapsed while taking infliximab. Patients may be given an initial dose of 160 mg on day 1 (given as four 40-mg injections in one day or two 40-mg injections daily for 2 consecutive days), followed by 80 mg two weeks later (day 15). After a further two weeks (day 29), a maintenance dose of 40 mg every other week may be started. Alternatively, UK licensed product information advises that patients at risk of adverse effects may be given 80 mg initially, followed by 40 mg 2 weeks later; thereafter, usual maintenance doses may be given. A clinical response is usually seen within 12 weeks of starting treatment; those patients who relapse while on adalimumab may benefit from increasing the maintenance dose to 40 mg every week.

In the treatment of moderate to severe chronic **plaque psoriasis** in patients unresponsive to, or intolerant of, conventional systemic therapy including phototherapy, the recommended initial dose of adalimumab is 80 mg subcutaneously; this may be followed by a maintenance dose of 40 mg subcutaneously on alternate weeks, starting 1 week after the initial dose. A clinical response is usually seen within 16 weeks of starting treatment.

For the uses of adalimumab in children, and recommended doses, see below.

Administration in children. In the USA, adalimumab is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 4 years and above: it may be used alone or with methotrexate. The dose is calculated according to weight and is given subcutaneously: those weighing 15 kg to less than 30 kg should be given 20 mg every other week, while heavier children may receive 40 mg every other week.