Drugs used to treat joint and muscle disease

David G Lambert

Abstract

Joint disease: Arthritis can be simply broken into osteoarthritis and rheumatoid arthritis (RA). Osteoarthritis is treated with symptomatic pain relief and surgery. RA is a chronic autoimmune disease that causes inflammation of joints (leading to their destruction), tissues around joints and other organ systems. Treatment (for pain) of RA in the first instance is with non-steroidal anti-inflammatory drugs, with second-line treatment using disease-modifying antirheumatic drugs (DMARDs). DMARDs are a disparate group and include methotrexate, D-penicillamine, sulphasalazine, gold salts, antimalarial drugs and immunosuppressant drugs. The newer class of 'biological' DMARDs includes etanercept (tumour necrosis factor α (TNF-α) receptor –immunoglobulin G chimera), infliximab (monoclonal anti-TNF-α antibody), anakinra (interleukin 1 receptor antagonist) and rituximab (an anti-CD20 antibody that depletes B cells).

Muscle disease: Myaesthenia gravis is an autoimmune disease targeted to muscle type nicotinic receptors. Treatment is based on improving neuromuscular function by: (i) increasing acetylcholine concentrations with neostigmine and pyridostigmine; (ii) immunosuppression; (iii) thymectomy; and (iv) plasmapheresis. General muscle spasticity can be caused by a wide range of conditions including multiple sclerosis, cerebral palsy, Parkinson's disease and secondary to stroke. This can be treated centrally with baclofen, tizanidine and benzodiazepines or peripherally with dantrolene. Botulinum toxin inhibits the exocytosis of acetylcholine-containing vesicles and can be used for cervical dystonia, strabismus, blepharospasm, severe axillary hyperhidrosis and cosmetic procedures.

Keywords Arthritis; disease-modifying antirheumatics; gout; immunosuppressants; joint disease; muscle disease; myasthenia gravis; NSAIDs

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- list the main joint and muscle diseases and their treatments
- describe the treatment options for arthritic disease, myasthenia gravis and muscle spasticity

Joint disease

There are several classification systems available for joint disease (Figure 1). The simplest is inflammatory and non-inflammatory. Arthritis is a general term used to describe painful conditions of joints and bones. There are many types of arthritis, including osteoarthritis, rheumatoid, spondylitis, gout and psoriatic arthritis, Reiter's syndrome and lupus. Arthritis is the most common long-term condition in the UK, affecting 20% of adults (approximately 387,000 with rheumatoid). A similar pattern is seen in Europe as a whole (100 million with one form of arthritis) and in the USA (~70 million with arthritis, ~2 million with rheumatoid).

Osteoarthritis

This is the most common joint disease and is often described as a disease of wear and tear. This disease affects around 8.5 million people in the UK alone, is more common in women and those who are overweight and affects a range of joints (knees, hips, hands and neck). There are important anaesthetic consequences relating to a reduced range of movement when the neck is affected. Typical degenerative changes include a thinning of joint cartilage, growth of osteophytes and increased synovial fluid production. Typical presenting symptoms are pain, joint stiffness, swelling and a reduced range of joint movement. Treatment options include pain control with non-steroidal anti inflammatory drugs (NSAIDs) and surgery of the affected joint(s).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is autoimmune in origin, more frequent in women, has a peak incidence in the 40- to 60-year age group and causes chronic inflammation of joints (leading to their destruction), tissues around joints and other organ systems. Multiple joints are involved and the symptoms can relapse and remit. Approximately 80% of patients are seropositive for rheumatoid factor (RF). Other blood results are consistent with an immune cause and include increased erythrocyte sedimentation rate, C-reactive protein and antinuclear antibodies. There are guidelines for the management of RA from the British Society for Rheumatology and British Health Professionals in Rheumatology.[1] These guidelines contain a comprehensive disease management algorithm for the first 2 years.

Pathogenesis: a basic understanding of the pathogenesis of RA is required to appreciate the current treatment strategies.[2] The initial stimulus for the production of RA is largely unknown, although an infectious 'trigger' may be present. The presence of this 'trigger' recruits a population of T cells, which interact with B cells and macrophages. Interaction with B cells results in the production of several antibodies; one of the more important is RF, which is involved in the diagnosis of RA, via a range of cytokines and cell–cell contact, activated T cells interact with macrophages that go on to produce interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α). Activation of macrophages and the production of these two cytokines is one of the main events that lead to a chronic inflammatory condition. IL-1 and TNF-α then interact with synovial fibroblasts, and chondrocytes

David G Lambert *BSc(Hons) PhD FRCA is Professor of Anaesthetic Pharmacology at the University of Leicester, Department of Cardiovascular Sciences, Division of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester, UK. Conflicts of interest: none declared.*

Please cite this article in press as: Lambert DG, Drugs used to treat joint and muscle disease, Anaesthesia and intensive care medicine (2018), https://doi.org/10.1016/j.mpaic.2018.01.008

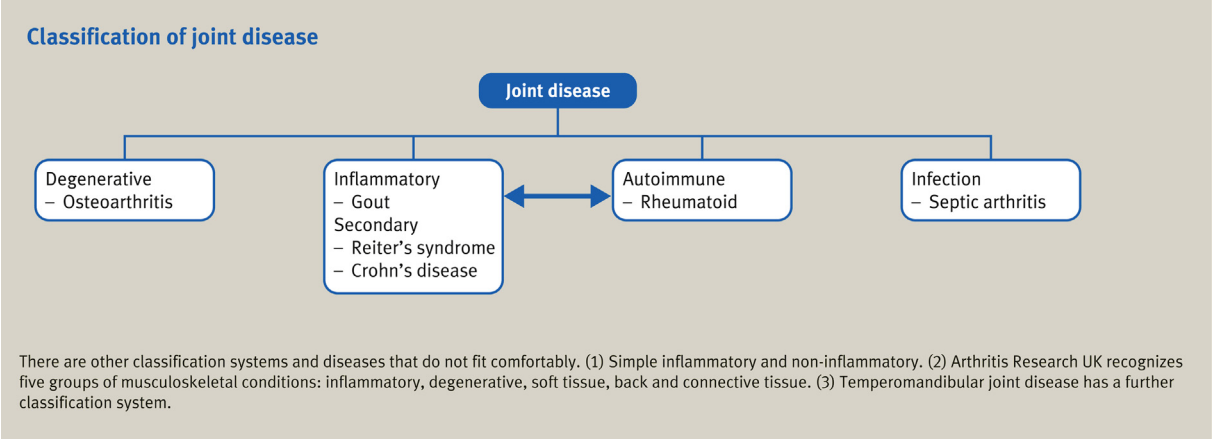

Figure 1

in joint cartilage and osteoclasts in joint bone tissue. This ultimately leads to joint erosion and destruction. The linkage of these events to joint erosion/destruction is unclear, but the matrix metalloproteinases (MMPs) and aggrecanases are involved. These are enzymes capable of degrading extracellular matrix proteins. A schematic representation of the basic pathology and sites of current clinical intervention are shown in Figure 2.

Treatment: this can be broken down into first-line use of NSAIDs for symptomatic (pain) control, second-line use of disease-modifying antirheumatic drugs (DMARDs), and newer 'biological' therapy. This last class could be considered as biological DMARDs.

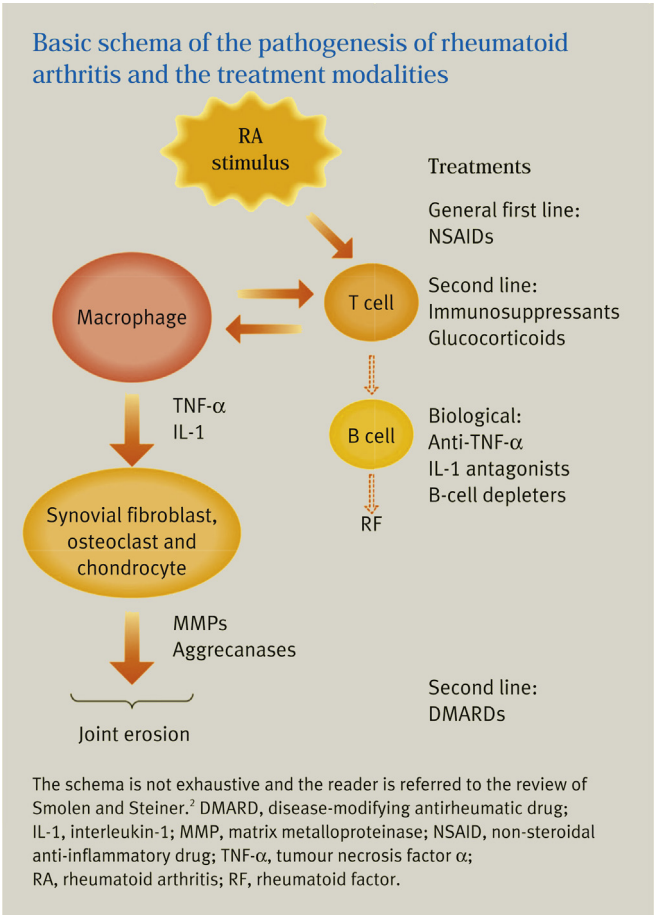

Figure 2

First line — NSAIDs are the current first-line treatment. These variably block cyclo-oxygenase (COX) 1 or 2 and reduce prostaglandin synthesis. This reduces pain, but has little effect on the immunological basis of the disease itself.

Side effects: all NSAIDs are associated with gastrointestinal (GI) toxicity. The Committee on Safety of Medicines classifies upper GI toxicity as highest for azapropazone and lowest for ibuprofen (piroxicam, ketoprofen, indometacin, naproxen and diclofenac are intermediate). Therefore, ibuprofen (as a non-selective COX inhibitor) should be used where appropriate. Although the risk of GI toxicity is reduced for COX-2-selective NSAIDs (e.g. the 'COXIBs'), there is an increased risk of thrombotic events. For this and subsequent side-effect descriptions, the reader is advised to consult the *British National Formulary* and product information sheets.

Second line (DMARDs) — As the name suggests, this group of pharmaceuticals modifies the inflammatory and destructive progress of the disease. It is a highly disparate group of compounds with complex (and often unproven) modes of action. This group includes methotrexate, D-penicillamine, sulphasalazine, gold salts, antimalarial drugs and immunosuppressant drugs. The evidence for DMARD use is to treat early and in combination. The current gold standard with which all other DMARDs are compared is methotrexate. The presumed site(s) of action and an estimate of clinical efficacy of the major DMARDs are illustrated in Table 1.

Side effects: these are variable and agent specific. Methotrexate produces the fewest side effects, which include nausea and vomiting, skin rashes and a range of blood test abnormalities. D-Penicillamine produces nausea and vomiting, anorexia, skin rashes and a range of blood test abnormalities. Sulphasalazine is a combination of salicylate and a sulphonamide, so reactions typical of sulphonamides are present and include GI disturbance, headache and general malaise. Gold salts can produce serious toxic effects, including hepatitis, peripheral neuropathy and encephalopathy. In addition, skin rashes and mouth ulcers are reported. Antimalarial drugs produce nausea and diarrhoea. Immunosuppressant drugs produce a range of effects specific to the agent but include increased risk of infection,

Please cite this article in press as: Lambert DG, Drugs used to treat joint and muscle disease, Anaesthesia and intensive care medicine (2018), https://doi.org/10.1016/j.mpaic.2018.01.008