

Clinical Trials in Rheumatoid Arthritis and Osteoarthritis

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Clinical Trials in Rheumatoid Arthritis and Osteoarthritis
David M. Reid and Colin G. Miller

David M. Reid • Colin G. Miller
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Clinical Trials in Rheumatoid Arthritis and Osteoarthritis

 Springer

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Chapter 1

Introduction

David M. Reid and Colin G. Miller

Why a Book About Clinical Trials in Rheumatoid Arthritis and Osteoarthritis?

From an etiology of disease perspective, a book on rheumatoid arthritis (RA) and osteoarthritis (OA) is a strange combination; however, from a clinical trial perspective, the primary end points are very similar. The primary end points in both disease states are imaging and serum or urine biomarkers as recognized by the U.S. Food and Drug Administration (FDA). The FDA guidance documents for OA [1] refer to the RA guidance documents for the imaging end points [2]. During the writing of this book, the Osteoarthritis Research Society International (OARSI) has teamed up with the Outcomes Measures and Evaluation in Rheumatoid Arthritis Clinical Trials (OMERACT) to create the OMERACT-OARSI working group. This is an obvious recognition of similar end points of the disease states.

The evolution of the trials in RA and OA is at an interesting point in time. There have been a number of successful therapeutic disease-modifying agents that have been developed and are now on the market for RA. The same is not true for OA, where at the time of writing there have been no successful FDA submissions for a disease modifying osteoarthritis anti-rheumatic drug (DMOAD), partly due to a lack of compounds and partly due to the challenges of running the trials. With RA, there is now a standard pattern and expectation for performing these trials with three anti-TNF- α and one anti-B-cell monoclonal antibody products on the market in a number of indications and many more to follow. For OA, the one large trial testing a potential DMOAD, using the bisphosphonate risedronate [3], sadly missed its primary end point. There are now a handful of studies evaluating glucosamine and chondroitin sulfate in both the United States and Europe [4, 5]. The first results are not only suggestive of a potential positive outcome but also more importantly demonstrate that with careful controls, a study in OA looking at joint space narrowing can be achieved (see Chapter 14).

D.M. Reid

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OA is a crippling disease that has approximately 10 times the prevalence of RA, and there is a huge unmet medical need for good drugs to halt disease progression. This is not to minimize the pain of RA; rather, the lessons learned from the RA field can be applied to OA.

Clinical trials are requiring more and more rigor, and the specific end points are becoming more complex, with an increasing and bewildering number of regulatory hurdles. This is the case with trials in RA and OA. The similarity of design makes the therapeutic combination come together. This book is intended for those new to conducting clinical trials in these areas: a handbook or a “how to.” It is not intended as an all-encompassing text on the results of those studies that have gone before or a thorough in-depth analysis of how to get through the regulations like the Code of Federal Regulations (CFR 21 Part 11, Electronic Records and Use of Electronic Signatures) [6]. This is the second book in the series (the first one being *Clinical Trials on Osteoporosis*) and it follows a similar format, allowing the reader to be able to read each chapter in isolation or to put the pieces together to obtain an overall picture. As with the book on osteoporosis, this book is also unique in that it brings together both the clinical trial aspect and the therapeutic aspect into one volume.

How This Book Works

The aim of this book is to lead the research through all the stages of a clinical trial. The first part covers background to current and some future therapies for RA and OA (Chapters 1 and 3), and the second part examines study design (Chapters 4 to 7) and the pretrial phase including ethical considerations specific to trials in RA and OA (Chapter 7).

The third part (Chapters 8 to 11) looks at the day-to-day running of the trial from the four main constituents involved in patient collection and data management: the sponsor, the site, the central blood or biomarker lab, and the central imaging core lab. It is interesting to note that the primary end points of biomarkers, be they serologic or imaging, are all now processed through independent third-party groups as a *de facto* standard. This would not have been the case 15 years ago.

The fourth part (Chapter 12) covers data analysis and presentation and includes a guide to writing a paper for a peer-reviewed journal to a standard that will ensure that readers will gain full benefit from one’s trial and the results will be easily included into subsequent meta-analyses.

The final part examines imaging end points and biochemical markers for both RA and OA (Chapters 13 to 16) and describes new possible end points of pharmacogenomics (Chapter 17) and pharmacoeconomics (Chapter 18).

We have attempted to use standard terminology throughout the book. This includes the sponsor (usually a pharmaceutical company who is funding the research), the contract research organization (or CRO), which is a company responsible for administering the trial, assuring the quality of the data, analyzing the data, and producing the final report. A clinical research associate (CRA) is the

representative of the sponsor or CRO who liaises between the CRO and each site participating in the trial. The investigator is the researcher at the local site who has responsibility for recruiting research subjects and running the study locally. We have chosen to refer to those taking part in clinical trials as *subjects* rather than *patients* for the very reason that many of them are not ill but are normal women and men. The drug under investigation is usually under development by the sponsor and is known throughout the book as the new molecular entity (NME).

Most chapters contain many references to other source material. These allow the reader to take any of the issues covered in the book to greater depth. As always, there are many abbreviations in the book, thus a glossary is given as an appendix.

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Chapter 2

Historical and Current Perspectives on Management of Osteoarthritis and Rheumatoid Arthritis

Shirish Dubey and Adewale O. Adebajo

Historical and Current Perspectives on Management of Osteoarthritis

Osteoarthritis (OA) is a slowly evolving but active disease of degeneration of the articular cartilage associated with symptoms of joint pain, stiffness, and limitation of movement. Typically, these symptoms tend to be worse with weight bearing and activity and improve with rest. Physical examination often reveals tenderness on palpation, bony enlargement, crepitus on movements, and limitation of joint movement. OA can occur in any joint but is most common in the hip, knee, and the joints of the hand, foot, and spine. OA is the most prevalent disease in our society and the second most common cause of disability in the elderly in the Western world, second only to cardiovascular disease [1]. In fact, more than 75% of persons above 70 years of age show some radiographic evidence of OA [2]. The World Health Organization (WHO) figures of worldwide estimates are that 9.6% of men and 18% of women aged more than 60 years have symptomatic OA [3]. The prevalence of OA increases with age because the condition is not reversible. Men are affected more often than women among those aged less than 45 years, whereas women are affected more frequently among those aged more than 55 years [4]. The prevalence of OA is only likely to rise further, due to a variety of reasons. Life expectancy has steadily increased over the years and continues to do so. The triad of increasing numbers of elderly people, obesity, and lack of exercise plaguing Western society at the moment is likely to have a significant effect on the burden of OA facing people and society in the next few decades.

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Historical Aspects

Perhaps the earliest descriptions of OA were provided by Heberden and Haygarth in the 19th century [5, 6]. In the 1930s and 1940s, Stecher showed that there were two forms of this disease, idiopathic and posttraumatic [7]. It was in the 1950s that the link between Heberden’s nodes and large joint OA was established with the publication of a paper by Kellgren and Moore [8]. The first x-ray grading system was developed in the 1950s by Jonas Kellgren and John Lawrence [9]. Lawrence led the application of this to epidemiology leading to the observation of discordance between radiographic and symptomatic OA [10]. Surgical options were pioneered as early as the 1950s and 1960s. John Charnley [11] and George McKee [12] both published their landmark papers during the 1960s, which transformed the surgical management of these patients.

Predisposing Factors

A variety of factors are recognized as predisposing factors for individuals with OA. These are summarized in Table 2.1.

Pathogenesis

OA is a dynamic process with intermittent progression characterized by an adaptive response of synovial joints to a variety of stresses. One of the first changes in OA appears to be cartilage loss. The cartilage normally consists of proteoglycans and glycosaminoglycans in the framework of type 2 collagen. There is a progressive depletion of the cartilage proteoglycan in the early stages of OA, leading to a net loss of matrix from the cartilage [13]. This in turn leads to a cascade of events including decrease in hyaluronic acid content, changes in the enzymatic cleavage of

Table 2.1 Predisposing factors for OA

Age
Female gender
Genetic predisposition of the individual
Previous trauma
Mechanical factors like malalignment
Previous or current occupation (e.g. farming, miners, jackhammer operators, etc)
Previous inflammatory arthritis
Biochemical and metabolic abnormalities (e.g., pyrophosphate arthropathy)
Exercise, particularly for professional sports persons
Obesity
Nutritional (low Vitamin C and Vitamin D levels)

Source: Adapted from Felson DT. Epidemiology of osteoarthritis, pages 9–14; in Osteoarthritis. Eds Brandt KD, Doherty M, Lowmader LS; Oxford University Press, 2003, 2nd ed.

proteoglycans, and increase in minor collagen types leading to structural and functional deterioration of the cartilage. Certain enzymes play a vital role in this process of breakdown of cartilage [14, 15], and these include the matrix metalloproteinase enzymes (MMPs). Collagenase (MMP-1) appears to have a significant role in this, as there is a correlation between the levels of collagenase and the severity of cartilage lesions in OA [16, 17]. A number of inhibitors of MMPs have also been identified with tissue inhibitors of metalloproteinase-1 (TIMP-1) and TIMP-2 being the most common in humans [18, 19]. This disease process that begins in the articular cartilage eventually involves the surrounding bone, the synovium, and the surrounding soft tissues. Often, there is evidence of bony sclerosis that is seen on radiographs [20], but after the initial stages of cartilage degeneration, there may be a delay of many years before any symptoms appear or there is radiologic evidence of OA. At least in part, this is due to lack of innervation of the cartilage whereas the surrounding structures, which include the periosteum, subchondral bone, and the joint capsule, appear to be richly innervated.

Treatment of OA

The goals of contemporary management of a patient with OA include control of pain and improvement in function as well as quality of life [21]. A number of issues need to be considered to decide the optimum management of a patient with OA, including level of pain and discomfort, level of disability, comorbidity, the joint involved, and the degree of radiologic damage [22].

A suggested protocol for managing OA is shown in Figure 2.1.

Nonpharmacological Therapies

A number of nonpharmacologic interventions are available for patients with OA and form an integral part of the treatment plan for these patients. Some of these include patient education therapies that are available for these patients include patient education, self-management programs, weight loss (if overweight), aerobic exercise programs, muscle strengthening exercises, medial taping of the patella, appropriate footwear, occupational therapy, joint protection and energy conservation, and assistive devices for ambulation or activities of daily living [21]. There is considerable evidence to suggest that nonpharmacological options are useful not only early but also later on in the course of the disease and help to reduce disability [23–25].

Pharmacological Therapy

Analgesics

Generally, pharmacological options should be used in addition to nonpharmacological measures [26]. For many patients, simple painkillers like paracetamol or

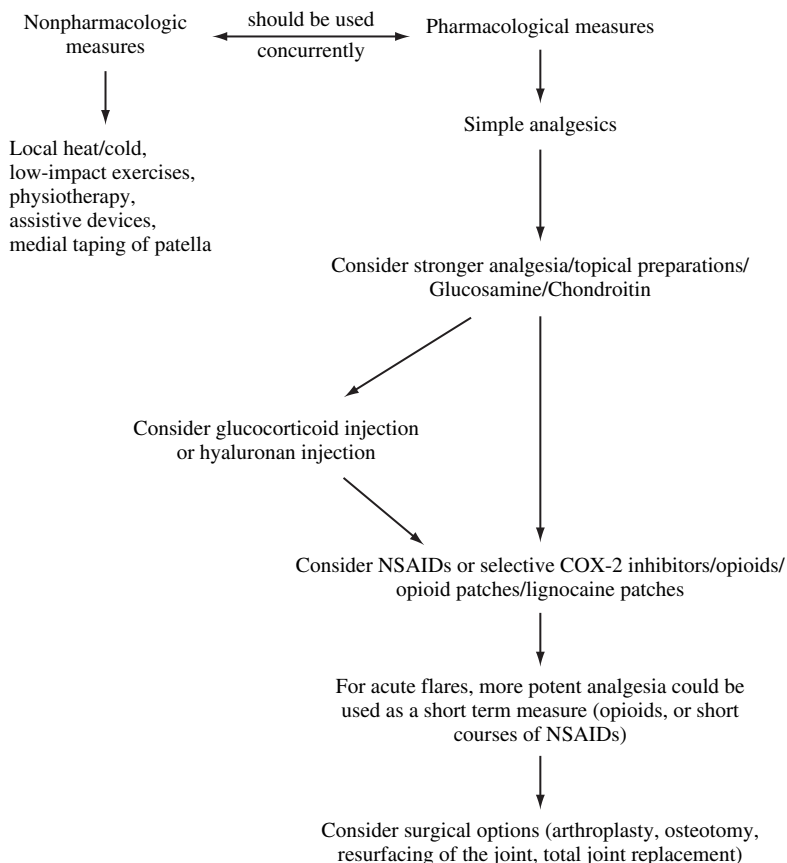


Fig. 2.1 Suggested protocol for managing osteoarthritis

acetaminophen are enough to provide significant symptom relief. Quite often for mild to moderate pain, the benefit to patients from simple analgesics is comparable with that from nonsteroidal anti-inflammatory drugs (NSAIDs) [27–29]. A meta-analysis of trials comparing simple analgesics with NSAIDs in patients with knee OA did find that NSAID-treated patients had significantly greater improvement in both pain on rest and pain on motion [30]. For moderate to severe pain, simple analgesics might not be sufficient and these patients would benefit from combination of simple analgesics with low-dose opioids, semi-synthetic opioids, transdermal opioids, or NSAIDs. There is some evidence to support the use of Buprenorphine patches and Lignocaine patches in these patients [31, 32].

Paracetamol and acetaminophen should be used with caution in patients with existing liver disease and avoided in patients with chronic alcohol abuse. These

drugs can also prolong the half-life of warfarin, and careful monitoring of the INR is necessary in these patients.

NSAIDs

In some patients, the combination of nonpharmacological interventions and simple analgesics will not be enough to optimally control symptoms. In this group of patients, additional pharmacological agents should be considered; most commonly this will be in the form of a NSAID. The choice of the NSAID agent depends on a number of factors including the age of the person, comorbid medical conditions, history of upper gastrointestinal (GI) bleeding or ulcers, and anticoagulant and steroid use. In these cases, it might be safer to use selective cyclooxygenase (COX)-2 inhibitors rather than nonselective NSAIDs. The National Institute of Clinical Excellence in the United Kingdom has issued guidelines for the use of selective COX-2 agents [33]. Selective COX-2 inhibitors have the advantage of reduced risk of GI side effects alongside comparable efficacy compared with the traditional NSAIDs [34–38]. Another advantage of the selective COX-2 inhibitors is that they have no effect on platelet function, which is a major advantage during the perioperative period, as well as for patients on warfarin [39]. The common traditional NSAIDs include ibuprofen, diclofenac, naproxen, indomethacin, piroxicam, and so forth. The common selective COX-2 inhibitors include celecoxib, etoricoxib, meloxicam, parecoxib, and etodolac. NSAIDs, both selective and nonselective, have to be used with caution because of certain common side effects in patients with hypertension, congestive heart failure, or renal impairment. Severe renal impairment is a contraindication for use of NSAIDs.

Recently, the cardiovascular safety of the selective COX-2 inhibitors has received a lot of attention. Various studies involving rofecoxib and valdecoxib (which were consequently withdrawn from the market), celecoxib, and parecoxib have shown an increased vascular risk mainly in the form of myocardial infarctions and strokes. Consequently, these drugs are now used more cautiously. The cardiovascular safety of standard NSAIDs has also received some attention recently, and there is now considerable evidence to suggest that standard NSAIDs share the vascular risk with selective COX-2 inhibitors [40]. Hence the Medicine and Healthcare Products Regulatory Agency (MHRA) recommends that ‘the lowest effective dose of the NSAID should be used for the shortest period of time’ [41].

Other Conservative Treatments

In patients with OA of the knee, topical analgesia is also an option. This could be in the form of a nonsteroidal gel, for example piroxicam gel, or in the form of capsaicin cream [41]. In some patients, this combination will still not be enough to provide adequate pain relief. In such patients, alternative analgesics could be used,

including opioid analgesics like codeine phosphate [28] or synthetic opioids like tramadol. Tramadol, a synthetic opioid that inhibits reuptake of noradrenaline and serotonin, is a centrally acting analgesic used for treating moderate to severe pain. It tends to have fewer side effects than would normally be associated with opioids, such as drowsiness, constipation, and respiratory depression. Its efficacy has found to be similar to ibuprofen in OA and is a useful adjunct [42, 43].

Intra-articular Injections

An alternative approach in the management of joint pain would be the use of intra-articular therapy. This could be in the form of glucocorticoid injections (particularly if there is evidence of joint effusion) or in the form of hyaluronic acid injections. The mechanism of action of hyaluronic acid appears to be unclear as the duration of benefit exceeds its synovial half-life. Proposed mechanisms include inhibition of inflammatory mediators such as cytokines and prostaglandins, and stimulation of cartilage matrix synthesis. In clinical trials, patients receiving intra-articular hyaluronic acid preparations had significantly greater pain relief than that seen with intra-articular injection of placebo and comparable with that seen with oral NSAIDs [44–46]. The extent of pain relief was similar to that experienced by patients treated with intra-articular glucocorticoid [46]. Intra-articular hyaluronic acid therapy is indicated for use in patients who have not responded to a program of nonpharmacological therapy and simple analgesics and could also be used in patients in whom nonsteroidals are contraindicated. However, real-life experience from use of hyaluronic acid therapy is not as positive as would be indicated from the trials alone.

Intra-articular glucocorticoids can be extremely useful in the treatment of patients with OA, particularly in the presence of a joint effusion [47]. In animal experiments, intra-articular glucocorticoids have demonstrated a protective effect with reduction of cartilage erosions and osteophyte size [48, 49]. There is, however, very little data from randomized, double-blind, placebo-controlled clinical trials in humans. Despite this, most clinicians have had experience of some benefit in patients with OA with the local administration of glucocorticoids. The difficulty lies in accurately predicting which patients will benefit with this form of therapy. Furthermore, repeated injections into the same joint tend to show diminishing response, although the reasons for this clinical phenomenon are unknown. The usual recommended dose of triamcinolone is 5 to 10 mg for a small joint such as the finger or thumb, 10 to 20 mg for joints like the ankle, wrist, and elbow, and 30 to 40 mg in a large joint like the shoulder or knee.

Glucosamine and Chondroitin

A meta-analysis of the evidence for use of glucosamine and chondroitin performed by McAlindon et al. [50] revealed moderate to large effects for these drugs in the treatment of hip or knee OA. Both glucosamine and chondroitin are derivatives of

glycosaminoglycans found in the articular cartilage. However, their mechanism of action is unclear as they cannot be absorbed from the gut intact [1]. One clinical trial demonstrated some efficacy in not only reduction of symptoms but also reduction in knee medial compartment changes over 3 years [51]. A Cochrane review of glucosamine and chondroitin as well as a review of knee OA by the European League Against Rheumatism (EULAR) have both recommended that there is reasonable evidence to support the use of these agents in the management of patients with OA [52, 53].

Experimental Treatments

Cod liver oil in the dose of 1000 mg daily has been found to have an effect on reducing the levels of enzymes responsible for degradation of the cartilage in patients undergoing knee replacement (data unpublished as yet). It is possible that in the future, cod liver oil may have a role to play in reducing the symptoms of OA or reducing progression. Other forms of treatment using delivery of anti-inflammatory cytokines or gene induction using gene transfer [54] may provide novel approaches to treatment of OA. It is possible that these therapies may provide the crucial breakthrough in terms of reducing the progression of disease, which has not been clearly established with any other form of treatment yet.

Surgical Treatments

Surgery of the joints in the form of joint replacement has been available for more than 40 years for the hip and 30 years for the knee. The numbers of knee prostheses are increasing more than the number of hip prostheses, such that the demand for both is now about equal. Joint replacement, however, is not the only surgical option available to patients with OA. A number of other options are available, particularly for the younger patients; these include surgical repair and cell and tissue transplantation. In the hip, surface replacement has been introduced [55], and in the knee, arthroscopic osteotomy [56], interpositional spacers [57], and unicompartmental knee arthroplasty [58] are all options.

The primary purpose of joint surgery is to relieve pain and restore function. Two surgeons in the 1960s, John Charley and George McKee, pioneered hip replacements. The former introduced metal-on-polyethylene hip prostheses fixed with cement [59], and this was the mainstay of hip replacements for about 3 decades, and the latter was responsible for metal-on-metal hip prostheses [12], which did not gain popularity until recently due to poor fixation. The Charnley approach was adopted as the standard approach for hips [60–63] and was applied to the knees as well. However, with time, the limitations of this started to become apparent, mainly the problems relating to cement and localized bone resorption [64–67] and fracture of femoral stems [68]. The risk of fracture was reduced by changes in the metal alloys and changes in the geometric design. However, the risk of localized bone resorption

persisted despite the advent of cementless prostheses. This was later recognized to be due to polyethylene wear debris [69–74]. Research into polyethylene stability revealed that the gamma irradiation in the presence of air was responsible for causing the compound to become unstable [75]. In addition, it gave rise to an increase in the wear rate as well as contributing to the osteolytic potential [76–78]. This has led to a new generation of designs and bearing materials for hip prostheses. Metal-on-polyethylene prostheses were developed for the knee and were commonly used for a number of years, with similar results.

All the above prostheses have a limited life span (of about 15 to 20 years), due to the inherent problems with them. However, for older patients with life expectancy of less than 20 years, these would still be perfectly acceptable options. For younger patients, there have been new developments including the use of ceramic femoral heads, ceramic-on-ceramic bearings, and metal-on-metal bearings that have led to alternative bearing options with better long-term results and less long-term risk of osteolysis [69,79–82]. For the knee, the major advance has been the introduction of a stable and oxidation-resistant polyethylene, which reduces the risk of delamination failure [82] and osteolysis [83–85]. Improved designs have also led to reduced wear and tear of these prostheses. Unicompartmental knee replacements have been shown to have some success in reducing the bone loss [58, 86], though long-term data are awaited. Recently, hip resurfacing has also been tried with some success [55]. Experimental work on cartilage culture and transplantation has shown some promise but is still more than a few years away from routine clinical use.

Summary

OA is primarily a disease of the cartilage later leading to ligament damage and instability of the joint. Management of this, the most common form of arthritis, involves a combination of nonpharmacological, pharmacological, and, in advanced cases, surgical options with early involvement of the multidisciplinary team. None of the therapeutic options are curative, but the aim of treatment is to reduce symptoms and improve quality of life. OA remains a significant health burden at the moment and is likely to remain so for the foreseeable future.

Historical and Current Perspectives on Management of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric polyarthritis that affects the small and large joints. The cardinal features of active RA include pain, swelling, morning stiffness (commonly more than an hour), warmth, redness, and limitation of function. Additional features present include malaise, tiredness, morning stiffness, and night pains. As RA progresses, additional features of chronic synovitis are superimposed. Chronic

synovitis with its attendant synovial proliferation and joint effusion can lead to instability of the joint. At the same time, destructive pannus destroys cartilage and subchondral bone. Joint deformities result and contribute to joint instability and malfunction, alongside distended joint capsule and torn ligaments and tendons. This leads to considerable disability among this group of patients, along with major economic loss. Consequently, RA can have a profound impact on patients, families, and society in general.

In about 20% of patients, the onset of RA is acute. Frequently, disease activity is at first intermittent, becoming more sustained over time. Some patients may have no more than a few months of discomfort, while others may become severely disabled. Spontaneous remission can occur, but is unlikely if the disease has been continuous for 2 or more years.

Medical management has most to offer in the early stages of the disease, when the aim is to prevent or control joint damage, prevent loss of function, and halt the systemic features of the disease. Various types of medication are used to achieve this aim. Simple analgesics are used for pain control, alongside anti-inflammatory drugs (NSAIDs). Other drugs used for control of systemic inflammation are labeled under the group called disease-modifying antirheumatic drugs (DMARDs). These drugs have also been known in the past as second-line drugs, remission-inducing drugs, and slow-acting antirheumatic drugs (SAARDs). Some of these drugs have been available for more than 50 years (e.g., gold, antimalarials, and corticosteroids), whereas others are relatively new, particularly the biologics, which will be discussed in greater detail in Chapter 12.

Evolutional History of Pharmacotherapeutics in RA

The past century saw considerable development in the pharmacological therapy of RA. This progress has been continued in this century with the increased usage and advent of the biologic agents. The 20th century began with the synthesis of salicylic acid, which was the first NSAID and led later to the discovery of other NSAIDs, including more recently the selective COX-2 inhibitors (discussed earlier). In the early part of the past century, salicylates were used extensively for pain relief and as antipyretics. This was subsequently studied in clinical trials in the 1960s [87] and the association with significant side effects led to the development of indomethacin, phenylbutazone, and other NSAIDs, which later became the mainstay of pain relief and anti-inflammatory activity. Along with this, other forms of treatment for RA were also studied, with reports suggesting good efficacy with intramuscular Gold in 1945 [88] and substance E (hydrocortisone) in 1949 [89]. At the same time, other drugs were being experimented with. These included sulfasalazine, which was first tried in 1948 [90], and antimalarials that were tried in the 1950s and 1960s, although there had been some history of use of chloroquine for joint problems from the 19th century [91]. D-Penicillamine was studied in some controlled studies in the 1970s [92–94], and methotrexate was added to the armory of RA

drugs, along with cyclophosphamide, azathioprine, and later ciclosporin (previously named cyclosporine). More recently, leflunomide has become available. Along with these developments, there have also been developments in the newer NSAIDs, particularly in the past decade with the advent of the selective COX-2 inhibitors. The selective COX-2 inhibitors are generally regarded as being safer than the traditional NSAIDs mainly because of a reduced rate of ulceration and bleeding from the gastrointestinal tract, although recent data has raised some concerns relating to the cardiovascular and cerebrovascular safety of these drugs, more so for selective COX-2 inhibitors, but also for the traditional NSAIDs.

Perhaps the biggest change in the treatment of RA lies not in the increased choice available to the doctors and the patients but in the manner in which these drugs are used. Traditionally, the treatment of RA revolved around control of symptoms with painkillers and NSAIDs, with the more “toxic” agents being limited to use after the former drugs had failed to control the arthritis (hence, the concept of second-line agents). With the increase in the knowledge about RA, availability of better instruments for measuring disease activity, better assessments for determining long-term prognosis, and the devastating effects of progressive disease on joint and general health, there is a marked change in the use of these drugs. Rheumatologists now use DMARDs early in the natural history of the disease and are less inclined to await untoward events before resorting to more powerful agents [95]. Perhaps the best indicator of current perceptions for treatment are the guidelines for management of RA published by the American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines (2002 update). These guidelines state very clearly that “the majority of patients with newly diagnosed RA should be started on a disease-modifying antirheumatic drug within 3 months of the diagnosis” [96]. Experience from the Early Arthritis Clinics across the world suggests that there is a therapeutic “window of opportunity” that exists before the inflammatory load becomes significant. Evidence would suggest a better prognosis for initiation of DMARDs in very early RA (within 3 months of onset of symptoms) compared with later early RA (up to 12 months from onset of symptoms) [97]. When early RA is treated aggressively, there appears to be a reduction in degree of joint damage, long-term disability and improves the chances of remission [98, 99].

Once a diagnosis of RA has been made, treatment begins by educating the patient about the disease and the risks of joint damage and disability, as well as discussion of the available forms of treatment and the risks and benefits of these. Patients should be referred to physiotherapists, occupational therapists, and social workers as part of a multidisciplinary approach. As it is quite difficult for patients to grasp all of these issues in one visit, it is preferable to give patients sufficient time to understand and reflect on the significance of the discussion, without delaying the initiation of treatment. Patient education is a continuous process based on patient and physician partnership. NSAIDs and glucocorticoids (intra-articular or low-dose oral) can be used in the meantime for symptom control. The majority of patients with newly diagnosed RA should be started on DMARD therapy within 3 months of diagnosis, and the trend is to start therapy even sooner in a bid to improved overall long-term prognosis. Treatment of RA is an iterative process, and continuous reassessment of patients is extremely important.

Initial Assessment of Patients with RA

Any patient suspected of having RA should undergo a baseline assessment that should include symptoms of active disease (history of joint pain and swelling, duration of morning stiffness, diurnal variation of symptoms), functional status, clinical evidence of synovitis, presence of extra-articular disease, radiographic damage, and baseline laboratory investigations. The baseline laboratory investigations include full blood count (FBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, renal function tests, liver function tests (including hepatic enzymes, alkaline phosphatase, and albumin), and urinalysis. In certain instances, a synovial fluid analysis may be deemed necessary to rule out other differential diagnoses like septic arthritis or crystal arthritis. The assessment of renal and hepatic function tests is necessary as a number of antirheumatic drugs (including NSAIDs) can cause renal and/or hepatic damage and may be contraindicated in the presence of impairment of these organs.

Along with these baseline laboratory investigations, the patient should be assessed for comorbid conditions, and a validated tool should be used for assessment of pain, disease activity, and quality of life [100, 101]. Poor prognostic markers should be identified. These include early age of disease onset, high titer of rheumatoid factor, elevated ESR, and swelling of more than 20 joints [102]. Extra-articular manifestations of RA include rheumatoid nodules, sicca syndrome, interstitial lung disease, eye involvement (episcleritis, scleritis, and, in later stages, scleromalacia perforans), pericardial involvement, and systemic vasculitis. These may indicate a worse prognosis. Antibodies to citrullinated peptides have recently been shown to have significant association with erosive disease [103]. Aggressive treatment with DMARDs should be initiated in patients with RA as soon as the diagnosis has been made to reduce the incidence and severity of joint damage.

Further Management of RA Patients

Once the diagnosis of RA has been made and the treatment commenced, the focus of the consultation shifts to determining whether there has been an improvement in the patient's condition and whether there is any continuing evidence of disease activity. Various assessments are useful in this regard. It is important to document duration of morning stiffness, severity of joint pain, presence of swollen and tender joints, as well as limitation of function. It is also worthwhile repeating at intervals the tools used for making the initial assessment of disease activity, pain and quality of life measures. Other indicators of progression or improvement include ESR, CRP, and repeat radiographs (not normally repeated at intervals of less than 12 months). It can sometimes be difficult to determine whether a decline in function is the result of inflammation, mechanical damage, or a combination of both. These distinctions are important, as treatment strategies will differ accordingly.

Although there are a number of markers of disease activity, one that has gained substantial acceptance in clinical practice appears to be the Disease Activity Score (DAS). The DAS-28 score forms the basis for defining disease activity in the UK,

Table 2.2 Criteria to define complete remission

-
1. Absence of symptoms of active inflammatory joint pain
 2. No morning stiffness
 3. No fatigue
 4. No synovitis on joint examination
 5. No progression of damage on sequential radiographs
 6. Normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
-

Source: From Pinals RS, Masi AT, Larsen RA, and the subcommittee for criteria of remission in RA of the American Rheumatology Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981;24:1308–15.

with regards to decisions about initiation of biologic agents. This is calculated on the basis of number of swollen and tender joints, ESR (or CRP), and global health assessment on the basis of a 100 mm visual analogue scale. Other measures that can be used to determine the functional status include Arthritis Impact Measurement Scales [104] and Health Assessment Questionnaire [105]. The American College of Rheumatology (ACR) has developed criteria for defining improvement [98] and clinical remission [106] in RA (see Table 2.2). Whereas these criteria have gained considerable acceptance for outcome assessment in clinical trials, they have not had the same degree of success in terms of their adoption in clinical practice. The ACR criteria for 20% clinical improvement (the ACR20) require a 20% improvement in the tender and swollen joint count, as well as a 20% improvement in three of the following five parameters: patient's global assessment, physician's global assessment, patient's assessment of pain, degree of disability, and level of acute-phase reactant (CRP). These criteria have been expanded to include criteria for 50% and 70% improvement measures (i.e., ACR50, ACR70). Other criteria, such as the Paulus criteria [105], have also been employed. Radiographic progression using the Sharp or the modified Sharp score [107–110] have been used as an outcome measure of joint damage. Another concept that has gained considerable ground recently is use of quality of life measures. Perhaps the best of these is the Quality Adjusted Life Years (QALY), which has been used by the National Institute for Clinical Excellence in the United Kingdom to evaluate the use of biologic agents.

Nonpharmacological Treatment of RA

There are a number of nonpharmacological options that play an important role in the treatment of patients with RA. Patient education is an extremely important aspect of management. Not only the patient but also the patient's family needs to understand the condition and become involved in the process of making decisions about treatment. If treatment does not fully control the disease, the patient may struggle emotionally as well as physically in adjusting to this chronic disease, its flares, and the concomitant loss of function. Rheumatologists, other physicians, and support staff (nurses, physiotherapists, occupational therapists, social workers, etc.) play important roles in educating the patient and the patient's family about the disease and providing ongoing supportive care. Organizations like the Arthritis Foundation

in the United States and the Arthritis Research Campaign in the United Kingdom are an important source of educational material and/or programs. A range of health professionals including nurses, physical therapists, occupational therapists, social workers, health educators, health psychologists, and orthopedic surgeons may also be involved in a multidisciplinary team approach to the comprehensive management of RA. For example, participation in dynamic and aerobic conditioning exercise programs in patients with RA improves joint mobility, muscle strength, aerobic fitness and function, and psychological well-being without increasing fatigue or joint symptoms [110–113].

Short periods for rest can form part of management, particularly in the presence of a flare. Interestingly, whole-body rest can decrease the general systemic inflammatory response and was one of the forms of therapy that was used relatively commonly until the past decade. A judicious use of exercise and rest is recommended so as to maintain full range of motion of joints.

Pharmacological Treatment of RA

Pharmacological therapy for RA often consists of combinations of NSAIDs, DMARDs, and/or glucocorticoids. The common DMARDs used are described in Table 2.3 along with their dosing schedules and efficacy.

Table 2.3 Dosages, approximate time to benefit and comparative efficacy of some common DMARDS

Drug	Approximate time to benefit	Efficacy	Usual maintenance dose
Abatacept	2–12 weeks	+ + +	10mg/kg intravenous infusion every 4 weeks
Adalimumab	Few days to 12 weeks	+ + + +	40mg subcutaneous every fortnight
Anakinra	2–12 weeks	+ +	30-150mg subcutaneous daily
Azathioprine	8–16 weeks	+ +	50-150mg/day
Ciclosporin	8–16 weeks	+ +	2.5-4mg/kg/day
D-penicillamine	12–24 weeks	+ +	250-750mg/day
Etanercept	Few days to 12 weeks	+ + + +	25mg subcutaneous twice a week
Hydroxychloroquine	8–24 weeks	+ +	200mg twice a day
Gold, oral	16–24 weeks	+	3mg twice a day
Gold, intramuscular	12–24 weeks	+ + +	50mg every 4 weeks
Infliximab (plus methotrexate)	Few days to 16 weeks	+ + + +	3-10mg/kg IV every 8 weeks;
Leflunomide	4–12 weeks	+ + +	10-20mg/day
Methotrexate	6–12 weeks	+ + +	Oral: 7.5-25mg once a week; Injectable: 7.5-20mg/week
Minocycline	4–12 weeks	+ +	100mg twice a day
Rituximab	12 weeks	+ + +	2 infusions of 1000mg each 2 weeks apart, repeated approx. every 40-60 weeks
Sulphasalazine	6–12 weeks	+ + +	1 gm two to three times a day

NSAIDs

The historical treatment of RA usually involved the use of NSAIDs to reduce joint pain, joint swelling, and morning stiffness. These drugs were used before the decision to start a DMARD was taken, however, now these agents are used much less commonly as an adjunct to DMARD therapy. These agents help to reduce pain and have anti-inflammatory properties but do not alter the course of the disease or prevent joint destruction. Furthermore, the use of this group of drugs is limited by their side effects, particularly GI toxicity, though the newer selective COX-2 inhibitors are thought to be less toxic to the GI tract. NSAIDs should not be used as the sole treatment for RA. A number of agents are available and the choice of which drug to use is probably dictated by a combination of factors including efficacy, safety, convenience, incidence of GI side effects, comorbidity, and cost. NSAIDs act by inhibiting one or both of the cyclooxygenase enzyme isoforms, COX-1 and COX-2, which are responsible for the production of prostaglandins. COX-1 is present in many cells, including platelets, cells of the gastric and intestinal mucosa, and endothelial cells. COX-2 is the enzyme that specifically appears to be involved in inflammation. COX-2 also appears to be produced in the kidneys; hence selective COX-2 inhibitors may not necessarily be safe from nephropathy. However, selective COX-2 inhibitors do tend not to have an effect on platelet function [114], which may be of benefit when considering GI bleeding but may be a drawback when looking at the vascular complications of RA. Studies comparing nonselective NSAIDs to selective NSAIDs suggest that selective COX-2 inhibitors have a significantly lower risk of serious adverse GI effects than do nonselective NSAIDs [114, 115]. However, cost constraints may limit the use of selective COX-2 inhibitors as first-line NSAIDs in other than high-risk patients. These risk factors include advanced age (65 years or more), history of ulcer, concomitant use of corticosteroids or anticoagulants, higher dosage of NSAID, use of multiple NSAIDs, or a serious comorbid illness [116]. Evidence would also suggest that the combination of a nonselective NSAID with a proton pump inhibitor can provide the same level of protection from GI bleeds as a selective NSAID, though there is very little difference in the cost [117, 118]. As selective COX-2 inhibitors do not have any effect on platelet function [114], in patients with a vascular risk, low-dose aspirin should be used, which unfortunately may reduce the gastroprotective benefit of using selective COX-2 inhibitors. Some studies have suggested that use of selective COX-2 inhibitors is associated with the increased incidence of thrombotic events such as myocardial infarction compared with traditional NSAIDs. Quite a few selective COX-2 inhibitors have now been shown to have adverse vascular complications when used in high doses for long periods, and the use of these drugs in the presence of established cardiovascular and cerebrovascular disease is not recommended. Recent MHRA guidelines state that 'NSAIDs should be used in the lowest effective dose for the shortest duration' in view of recent evidence of vascular complications with traditional NSAIDs (see section on NSAIDs in management of OA).

DMARDs

DMARDs should be considered in every patient with RA, either alone or in combination with NSAIDs and/or glucocorticoids. Although NSAIDs and glucocorticoids may alleviate symptoms, joint damage may continue to occur and to progress, though there is now some evidence to support the use of glucocorticoids in reducing radiographic progression of RA [119]. DMARDs have the advantage of reducing or preventing joint damage and preserving joint integrity and function. Ultimately, this leads to better quality of life and may even result in economic benefit by keeping patients working for longer and reducing the need for joint surgery. DMARDs have traditionally been used when the disease is not responding to conservative treatment with NSAIDs. This is no longer best practice. The commoner DMARDs include methotrexate, gold, leflunomide, D-penicillamine, cyclosporine, sulfasalazine, hydroxychloroquine, azathioprine, and the new biologic agents (Table 2.3). DMARDs differ from NSAIDs in that the onset of effect is usually delayed for at least a few weeks, and they have no analgesic effect. They appear to act on various molecules at different levels of the inflammatory cascade, but are generally not curative.

Considerable evidence exists to support the efficacy of DMARDs in the treatment of RA. Recently, emphasis has focused on the best combination of DMARDs and on retardation of joint erosions based on radiographic evidence. DMARDs generally are effective at reducing the rate of progression of joint erosions or destruction and can sometimes even cause remission of the disease (Table 2.2). This, however, is likely to be short-lived when these drugs are discontinued.

From time to time, RA patients will experience a flare in their disease despite the patient being on DMARDs. This should prompt a careful consideration of further options including increase of dose, addition of another DMARD, or even changing to another DMARD. In instances where the active disease is limited to a few joints, intra-articular injections of corticosteroids may have an important role. For patients with severe symptoms, systemic corticosteroid therapy may be indicated, either oral (low-dose oral prednisolone) or in the form of methylprednisolone intramuscularly or intravenously (pulses).

Methotrexate

Methotrexate (MTX) has become one of the most widely used DMARDs in the treatment of RA. Antifolates (aminopterin) have been tried as early as 1951 for nonmalignant disease [120], but the introduction of steroids took attention away from this group of drugs, which included the less toxic methotrexate. This was still used for psoriasis and an improvement in psoriatic arthritis was noticed as well, but it was not until the 1980s that MTX gained acceptance as a good option for treatment of RA. During the 1990s, the popularity of MTX appeared to grow

further, and it gradually became the drug of choice for most patients with RA. Recent trends would indicate that methotrexate is rapidly becoming the most common initial DMARD, especially for patients whose RA is more active. There are a number of reasons for this. MTX has an established track record in the treatment of RA but also has the advantage of being cheap, easy to administer, having one of the best efficacy-toxicity ratios, and appears to be the best drug from the point of view of long-term patient compliance [121, 122]. RA patients taking MTX are more likely to discontinue treatment because of adverse reactions than because of lack of efficacy [123]. As a result, MTX has become the standard by which new DMARDs are evaluated. Randomized clinical trials have not only established the efficacy of MTX in RA but also provided evidence to support the view that MTX retards radiographic progression. It is usually administered once a week with doses ranging from 7.5 mg to 25 mg, and the anti-inflammatory effect may be obvious within 3 to 4 weeks, though in some instances, it does take considerably longer. In some patients, absorption of MTX from the GI tract can be patchy and erratic, and these patients may benefit from parenteral administration of MTX.

Despite extensive research, the precise mechanism of action of MTX remains unclear. MTX does inhibit the enzyme dihydrofolate reductase and causes reduced leukotriene production and interleukin-1 expression. The efficacy of MTX does not appear to be affected by the administration of folic acid, which is used frequently to reduce the incidence of side effects associated with MTX. Patients with RA are considered to be at higher risk of vascular events [124], and MTX therapy is associated with an elevation of serum homocysteine levels [125]. Elevation of serum homocysteine can cause increased predisposition to vascular injury [126, 127]. Folic acid or folinic acid administration can reduce the elevation of serum homocysteine seen in these patients [128]. Both these effects (increase of homocysteine and response to folic/folinic acid) appear to be independent of the C677T mutation in the methyltetrahydrofolate reductase (MTHFR) gene [129]. Hence, folate supplementation is increasingly becoming considered a standard part of therapy for patients on MTX.

Adverse effects of MTX include stomatitis, nausea, diarrhea, and alopecia, all of which may decrease with concomitant folic acid or folinic acid [130–132]. Other side effects of MTX therapy include leukopenia, bone marrow suppression (both usually reversible on stopping the drug), pulmonary symptoms, including MTX pneumonitis and pulmonary fibrosis, and rarely liver fibrosis and cirrhosis. Though the risk of liver cirrhosis is low, the most frequent side effect of MTX is deranged liver enzymes, and these do need to be monitored closely. A liver biopsy is indicated when there is persistent derangement of liver enzymes despite discontinuation of treatment [133].

Relative contraindications for MTX therapy include preexisting liver disease, renal impairment, significant lung disease, or alcohol abuse. Serious or life-threatening pulmonary toxicity is rare but can occur at any time. MTX is potentially teratogenic and should be discontinued 3 to 6 months before attempting conception.

Hydroxychloroquine

Antimalarials have been used for the treatment of rheumatic diseases as far back as the early 19th century [91], but it was not until the 1950s and 1960s that they were evaluated as part of controlled studies. The general consensus on the use of these drugs would be that this group of drugs is at best moderately effective for control of RA [134–138]. It does, however, have a better risk/benefit ratio than azathioprine or auranofin.

Hydroxychloroquine (HCQ) is the least toxic of the quinolones, and perhaps the least toxic of the DMARDs. Its therapeutic action can be delayed; response is seen in the majority within 3 to 6 months, though optimal benefit can take 9 to 12 months [139]. HCQ alone does not appear to slow radiographic damage to joints, despite the significant impact of HCQ on long-term patient outcome when initiated early. Patients given HCQ do not need any specific laboratory monitoring but do need periodic ophthalmic checks for early signs of reversible retinal toxicity. Other side effects include dermatitis, nausea, epigastric pain, myopathy, and hemolytic anaemia. HCQ is normally used in doses of 400 mg daily (up to 6.5mg/kg/day), and its role in RA appears to be in early/mild disease and/or as background treatment in combination with other DMARDs. Particularly common combinations appear to be combinations of MTX, sulfasalazine, and HCQ [140–143]; MTX and HCQ [142]; and cyclosporine and HCQ [143]. HCQ is relatively safe during pregnancy and can be continued through pregnancy, although breast-feeding should be avoided.

Sulfasalazine

Sulfasalazine (SASZ) is one of the few drugs originally developed for treatment of RA and is another antifolate drug (though weaker than MTX). Several studies have demonstrated good benefit with SASZ in patients with RA [144–146], though the evidence on the efficacy of SASZ in retarding radiographic progression is conflicting. Clinical response with SASZ is usually apparent within 2 to 4 months. This drug also appears to have a better long-term tolerance than some other drugs used for treatment of RA (particularly gold), with 22% of patients continuing the drug after 5 years in one study [147].

SASZ appears to be generally well tolerated, though some patients develop unacceptable side effects mainly in the form of nausea and abdominal discomfort within the first few weeks of initiation of the drug. Traditionally, SASZ has been started off at 500 mg once daily with weekly increments of 500 mg until the full dose of 2 to 3 g daily has been reached. It is, however, debatable whether this schedule is necessary and in particular whether it reduces the risk of GI side effects. SASZ however, can cause leukopenia, particularly in the first year of treatment, and derangement of liver enzymes, and laboratory monitoring is essential. SASZ appears to be more popular in Europe, where it tends to be used more commonly both alone and in combination therapy with MTX and HCQ. SASZ can cause neonatal hemolysis, although

according to the *British National Formulary*, it could be continued in pregnancy with adequate folate supplementation.

Leflunomide

Several randomized controlled clinical trials have established leflunomide as an effective agent for control of RA, either as monotherapy or in combination with other agents [144, 148–153]. It tends to be particularly useful in patients who cannot tolerate MTX or cannot be given MTX because of chest problems. The benefit with leflunomide appears to be similar to that with MTX, both in terms of reducing disease activity and slowing radiographic progression. It can also be used in combination with MTX in the event of suboptimal disease control with MTX alone. However, in patients where the combination is being used, careful monitoring of liver function tests is essential, as both drugs are potentially hepatotoxic and do frequently cause derangement of liver enzymes [149, 151].

Leflunomide has a long half-life, and although loading dose was previously recommended, is rarely used now due to increased frequency of side-effects. The usual dose for leflunomide is 20 mg daily (10 mg daily for elderly patients). In addition, the drug tends to accumulate in the body, and in cases of toxicity or unacceptable side effects, leflunomide would need to be washed out with cholestyramine or activated charcoal. The common side effects of leflunomide include weight loss, hypertension, deranged liver function tests, and altered taste. Leflunomide is potentially teratogenic, and women taking leflunomide who wish to conceive must discontinue leflunomide and undergo cholestyramine or activated charcoal washout before attempting conception. Leflunomide should not be used in patients with obstructive biliary disease, liver disease, viral hepatitis, severe immunodeficiency, inadequate birth control, and rifampin therapy (which raises leflunomide levels).

Gold Salts

Gold compounds were first used in the 1920s to treat arthritis, and Forestrier's report in 1935 furthered this [154]. In 1960, the Empire Rheumatism Council published their double-blind trial, which suggested that gold salts were beneficial in about 60% to 80% of patients with RA. Gold compounds diminish the acute and chronic inflammatory response at a number of points in the inflammatory cascade. Several other studies have also proved the efficacy of gold salts [155–157]. Despite this, gold salts are not first-choice DMARDs, mainly due to the fact that oral gold is less effective [155, 156] and parenteral gold ideally needs to be administered on a weekly basis for the first 6 months. After this, the gold injection schedule can be reduced to fortnightly or monthly. Gold salts require regular monitoring, as risk of hematologic side effects is relatively high. Gold salts can also give rise to renal complications

like nephrotic syndrome, and urine monitoring for proteinuria is essential. Rash is common with an incidence of 15 to 30%, and can be so severe that gold salts may need to be permanently discontinued.

Ciclosporin (Previously Named Cyclosporine)

Ciclosporin is an immunosuppressant that can be used in RA both as monotherapy [158, 159] and in combination with other drugs [160]. Despite its undoubted efficacy, its use has been limited by its side-effect profile, which includes hypertension and renal impairment [161, 162]. Several drugs interact with ciclosporin and thus increase the risk of nephrotoxicity. Furthermore, ciclosporin is relatively expensive, and hence ciclosporin treatment is primarily confined to patients with refractory RA.

Other DMARDs

Azathioprine, a purine analogue myelosuppressant, has demonstrated benefits in RA but has limited effectiveness [156, 157, 163–165]. Recent data suggests that it is worth measuring serum thiopurine methyltransferase levels to assess the risk of developing bone marrow toxicity with azathioprine [166]. D-Penicillamine is also effective [92, 93, 156, 157], but its use is limited, in part, by an inconvenient dosing schedule (i.e., slow increases in the dosage) and rare but potentially serious complications, including autoimmune diseases, such as Goodpasture's syndrome and myasthenia gravis. Minocycline has recently been found to be effective in controlling RA in some randomized, double-blind, placebo-controlled trials [167–170]. Importantly, one trial showed long-term benefit of minocycline and a decrease in radiographic progression in a subset of patients who were positive for the human leucocyte antigen-DR4 shared epitope [171]. Further research is necessary before the role of minocycline in the treatment of RA is clearly defined.

Glucocorticoids

Glucocorticoids were used for arthritis as far back as the early 1950s (substance E; 1949) [89], and since then this group of drugs has always had a role to play in control of RA. A patient disabled by active polyarthritis may experience marked and rapid improvement in functional status within a matter of days after initiation of low-dose glucocorticoids (up to 10 mg of prednisolone daily). Indeed, in terms of its short-term efficacy, very few drugs can match the response obtained with glucocorticoids. Frequently, disabling synovitis recurs when glucocorticoids are discontinued, even in patients who are receiving combination therapy with one or more DMARDs. As a result, patients with RA may become functionally dependent on glucocorticoids and continue them long-term. There is some recent evidence to support the role of