Rheumatology: 7. Basics of therapy

Simon H.K. Huang

The case
Ms. R, a 48-year-old woman, consults her physician complaining of a 2-month history of gradually increasing pain in her right knee. The pain is worse when she squats, kneels and goes up or down the stairs. She has noticed painless swelling of several of her distal interphalangeal joints in the past year. Ms. R is otherwise healthy, has no morning stiffness or other systemic complaints, has not travelled recently and has no history of recent infection. On examination, the physician finds that the knee is slightly warm and swollen, and the patient has retropatellar pain and crepitus. Her distal interphalangeal joints are mildly tender on palpation and show osteoarthritic Heberden's nodes. A friend has told Ms. R that she should take glucosamine; another has recommended ibuprofen. Ms. R asks the physician what is wrong with her knee and what to take for the pain.

Dr. Huang is Clinical Associate Professor at the University of British Columbia, Vancouver, BC.

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The Arthritis Society salutes CMAJ *for its extensive series of articles on arthritis. The Society believes that this kind of information is crucial to educating physicians about this devastating disease.*

Series editor: Dr. John M. Esdaile, Professor and Head, Division of Rheumatology, University of British Columbia, and Scientific Director, Arthritis Research Centre of Canada, Vancouver, BC.

Before prescribing any treatment, it is important to establish clearly the patient's primary complaints and their underlying cause. When possible, treatment should be prescribed to treat the cause, rather than just the symptoms. The ideal treatment would reduce pain and inflammation, preserve range of motion and muscle strength, maintain function and, at the same time, be safe.

Basic therapy for patients with musculoskeletal pain includes nonpharmacologic, pharmacologic and alternative or complementary treatments. Ideally, treatment should be carried out by a team, with the active participation of the patient, family members and the family physician. The involvement of rheumatologists, orthopedic surgeons, psychiatrists, physiotherapists, occupational therapists, massage therapists, nurses, pharmacists, psychologists or social workers may be required.

Pharmacologic and nonpharmacologic methods complement each other in the treatment of musculoskeletal pain. Before drugs are prescribed, patients should be following an optimal nonpharmacologic program that includes patient education and physiotherapy or occupational therapy (see an upcoming article in this series on physical and occupational therapy by Bruce M. Clark). Pharmacologic treatment includes analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).

Analgesics

Acetaminophen is the first-line pharmacologic agent for people with noninflammatory musculoskeletal pain.[1,2] For patients with osteoarthritis of the knee, acetaminophen, 4 g/d, was found to be as effective as ibuprofen, 1200 or 2400 mg/d, when taken for 1 month.[3] Acetaminophen can be used as required for episodic pain, prophylactically before activities known to provoke pain or at a fixed dose of up to 4 g/d for constant pain. The optimal dose should be adjusted according to the patient's clinical response, namely, beginning at a low dose and increasing until pain relief is achieved. If symptoms are only partly controlled with a full dose of acetaminophen, other pharmacologic agents can be added as required or as a fixed dose.

For patients with inflammatory musculoskeletal pain, acetaminophen alone is rarely effective.[4]

No significant adverse drug interactions are associated with acetaminophen. It can be used safely by people with peptic ulcer disease, renal failure or a bleeding diathesis. However, it should be used with caution in those with pre-existing hepatic disease. All patients should be warned of the possibility of hepatic complications with alcohol ingestion.

Narcotic analgesics should be avoided in patients with chronic musculoskeletal pain. However, in acute severe musculoskeletal pain, such as that associated with vertebral compression fractures, sciatica from disc prolapse, or severe and acute exacerbation of underlying arthritis, narcotic analgesics can be used for short periods to maintain function and quality of life.

Nonsteroidal anti-inflammatory drugs

NSAIDs are the most frequently prescribed pharmacologic agents in the management of musculoskeletal pain and the first-line drugs in the treatment of inflammatory

musculoskeletal pain.[5] Currently, about 20 NSAIDs are available in Canada; these can be classified into several chemical groups (Table 1).

Although there are minor differences in the mechanism of action of NSAIDs, they are all inhibitors of the cyclo-oxygenase enzyme (COX); thus, they prevent the conversion of arachidonic acid into prostaglandins (Fig. 1). Prostaglandins have different effects on different tissues and organs. In the joints they induce and perpetuate inflammation by causing vasodilatation, allowing an influx of more inflammatory cells and mediators. In the upper gastrointestinal (GI) tract, prostaglandins protect the mucosal lining by reducing acid secretion and by increasing the production of mucus and bicarbonate. In the kidney they are necessary to maintain renal function when renal perfusion is reduced, and they are necessary for normal platelet function. Therefore, although nonspecific inhibition of prostaglandin synthesis is beneficial in terms of reducing inflammation and pain in the joint, it may cause upper GI, renal and platelet dysfunction.

Furthermore, although NSAIDs are effective in reducing symptoms, they do not reduce joint damage. Because of this and the potential for serious toxicity, they should be used at the minimum effective dosage, even for patients with inflammatory joint diseases.

NSAID selection

All NSAIDs have been shown to be approximately equivalent in efficacy and superior to placebo in the management of various types of musculoskeletal pain. According to some rheumatologists, certain NSAIDs appear to be more effective than others for selected rheumatic diseases. For example, indomethacin seems to be more effective for treating gout and osteoarthritis, whereas tolmetin, indomethacin and diclofenac appear to be more effective for treating spondyloarthritis.

Patients vary in their response to different NSAIDs. Therefore, physicians should become familiar with 1 or 2 preparations within each chemical group. Factors to be considered in NSAID selection for any patient include the underlying condition, the physician's familiarity with the drug, the drug's half-life, and the cost and availability

Table 1: Nonsteroidal anti-inflammatory drugs available in Canada

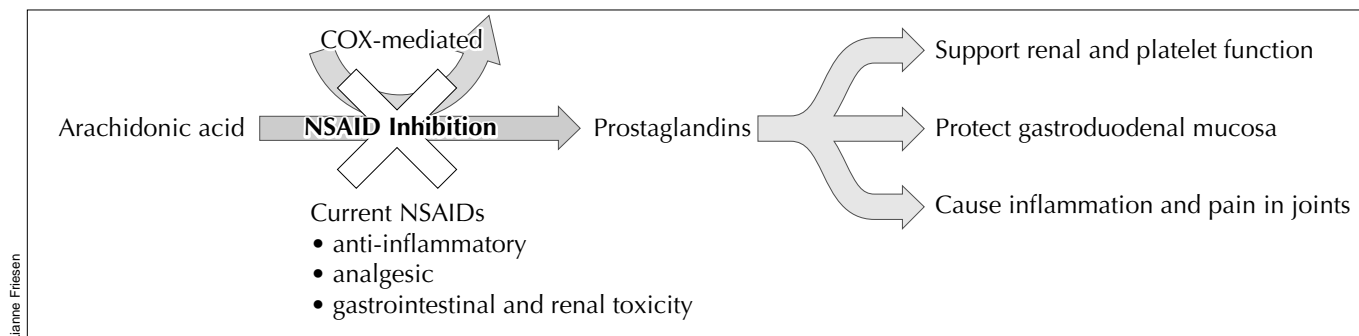| Chemical class	Generic name of drug (brand name)
Salicylates and derivatives	**Acetylated** Acetylsalicylic acid (Aspirin) **Nonacetylated** Diflunisal (Dolobid) Salsalate (Disalcid)
Oxicams	Piroxicam (Feldene) Tenoxicam (Mobiflex)
Naphthylalkanones	Nabumetone (Relafen)*
Pyranocarboxylic acids	Etodolac (Ultradol)
Proprionic acids	Ketoprofen (Orudis) Ibuprofen (Motrin) Naproxen (Naprosyn) Tiaprofenic acid (Surgam) Flurbiprofen (Ansaid) Fenoprofen (Nalfon) Oxaprozin (Daypro)
Phenylacetic acids	Diclofenac sodium (Voltaren) Diclofenac sodium plus misoprostol (Arthrotec)
Indoles	Indomethacin (Indocid) Sulindac (Clinoril) Tolmetin (Tolectin)
Pyrazoles	Phenylbutazone (Butazolidin)
Fenamates	Mefenamic acid (Ponstan)

*Pro-drug.

Fig. 1: Mechanism of action of NSAIDs. COX = cyclo-oxygenase enzyme, NSAIDs = nonsteroidal, anti-inflammatory drugs.

through a local formulary or insurance company. In acute arthritis, such as gout, full-dose NSAIDs should be started. For chronic musculoskeletal pain, the starting daily dose should be half the maximum, and the maintenance dose should be determined by assessing the benefits and side effects. When an NSAID has been tried at full dose for 2 weeks without satisfactory results, another NSAID from a different chemical class should be tried.

Different forms of the same drug are often available. For example, sustained-release, controlled-release, enteric-coated and suppository formulations may be available for many NSAIDs. Sustained-release and controlled-release formulations and NSAIDs with a long half-life may be more convenient because these are taken only once a day. Sustained-release, controlled-release and suppository formulations may be more effective in reducing morning stiffness in patients with inflammatory joint disease. Suppository and enteric-coated formulations may reduce upper GI symptoms of dyspepsia, but there is no evidence that they reduce serious upper GI complications.[6,7] In many instances the choice of formulation becomes one of personal preference and the preference of local third-party payers.

Side effects

The major side effects of NSAIDs, namely, upper GI toxicity, renal toxicity and platelet dysfunction, are related to the inhibition of the COX enzyme, which mediates the production of prostaglandins in the upper GI tract, kidneys and platelets. Etodolac and nabumetone, 2 of the newest NSAIDs available in Canada, have been found to have a slightly preferential inhibition of the COX-2 enzyme, one of 2 isoforms of COX, in the joint.[8–15] Salsalate is a weak COX inhibitor and may have a different mechanism of action.[16] In some studies,[17–19] etodolac, nabumetone and salsalate have been found to cause fewer endoscopically demonstrable upper GI ulcers. Enteric-coated, sustained-release, controlled-release and suppository formulations are still capable of inhibiting the production of prostaglandins in the upper GI tract and have been found to be associated with the same degree of endoscopically demonstrable lesions.[6,7,20,21]

Upper gastrointestinal toxicity

NSAIDs may cause dyspepsia by direct irritation of the upper GI tract or by altering intestinal motility. However, dyspepsia is not correlated with endoscopically demonstrable ulcers or with serious upper GI complications.[22] Dyspepsia is often transient. If dyspeptic symptoms persist, they can usually be controlled by using a different formulation of the same drug, such as enteric-coated, sustained-release, controlled-release or suppository; reducing the dosage; changing to a different NSAID; or adding an antacid, H_2-receptor antagonist or proton-pump inhibitor.

In the upper GI tract, prostaglandin E protects the

mucosal lining by decreasing acid secretion and by increasing bicarbonate and mucus production. By inhibiting prostaglandin production, NSAIDs have been shown to cause endoscopically demonstrable upper GI ulcers as well as other serious upper GI complications, including perforation, gastric outlet obstruction and clinically significant upper GI bleeding.[23] The prevalence, at any given time, of NSAID-induced endoscopically demonstrable upper GI ulcers is 15%–25%.[24] These lesions are usually asymptomatic. The rate of serious upper GI complications for patients with rheumatoid arthritis who are over the age of 50 years and have been taking an NSAID for 6 months is 1%.[23]

The risks of serious upper GI complications vary directly with increasing age, a history of upper GI ulcers and increasing number of concomitant medical illnesses, such as cardiovascular disease. If NSAID use cannot be avoided for these patients, misoprostol should also be administered. Misoprostol (200 µg, 2–4 times a day) has been found to be effective in reducing the incidence of gastric and duodenal ulcers;[25] a dose of 200 µg, 3 or 4 times a day, is effective in reducing serious upper GI complications.[23] As misoprostol can cause spotting, cramps, hypermennorrhea, menstrual disorder and dysmennorhea, it should be avoided in women who could become pregnant. The dosage of 200 µg, 3 or 4 times a day, is often associated with bloating, reflux, abdominal cramps or diarrhea. These side effects are often transient and are less common when the drug is taken with

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Key points

- Treatment of musculoskeletal pain should focus on the underlying cause. It should aim to reduce pain and inflammation, preserve range of motion and muscle strength, maintain function and be safe.
- Basic therapy may include nonpharmacologic, pharmacologic and alternative treatments.
- New forms of NSAIDs with a more specific site of action, which are now becoming available, will reduce the frequency of side effects, especially upper GI lesions.
- Although NSAIDs reduce inflammation and pain, their nonspecific inhibition of prostaglandin synthesis may cause upper GI, renal and platelet dysfunction.
- Acetaminophen is the first-line pharmacologic agent for patients with noninflammatory musculoskeletal pain.
- Physicians should become familiar with 1 or 2 NSAIDs within each chemical group to allow them to prescribe the best drug, formulation and dosage for a specific patient and to minimize side effects.
- Treatment should be carried out by a team of specialists and health care workers with the active participation of the patient, family members and the family physician.

food. When misoprostol is coadministered with an NSAID, it should be started at 200 μg daily with food and increased slowly to 2 or 3 times a day to reduce the likelihood of developing side effects.

H$_2$-receptor antagonists (e.g., "high-dose famotidine") and proton-pump inhibitors (e.g., omeprazole) have been shown to reduce endoscopically demonstrable gastric and duodenal ulcers;[26,27] however, their role in the prevention of serious upper GI complications is less clear.

Renal toxicity

In the kidney, prostaglandins induce dilatation of intrarenal vessels during periods of reduced renal perfusion. By inhibiting the ability of the kidney to compensate for reduced perfusion, NSAIDs may reduce glomerular filtration rates in patients with pre-existing renal disease, congestive cardiac failure and reduced intravascular volume and in patients taking diuretics. For these patients, if an NSAID cannot be avoided, periodic tests of renal function (including creatinine and electrolyte levels) should be carried out, especially when an NSAID is first started. The concomitant use of indomethacin and triamterene should be avoided, because it has been reported to cause renal dysfunction or hyperkalemia.

By reducing sodium clearance, NSAIDs may cause significant fluid retention in some patients. Renal toxicity may be somewhat lower with the newer NSAIDs such as salsalate, nabumetone and etodolac, because they may have a less inhibitory effect on renal prostaglandin production.

Platelet dysfunction

NSAIDs can interfere with platelet aggregation by inhibiting platelet thromboxane production. Some patients complain of easy bruising, although clinically this is not a major problem. For those taking anticoagulants concomitantly, platelet dysfunction may cause serious and even life-threatening GI bleeding.[28] ASA, by irreversibly inhibiting COX-1 in the platelets, will cause prolonged platelet dysfunction for up to 2 weeks. All other NSAID-related platelet dysfunction is reversible: platelet function is restored when the drug is cleared from the body.

Other side effects

NSAIDs may have clinically significant interactions with other drugs. By competing with protein-binding sites, NSAIDs may displace anticoagulants that are administered orally, hypoglycemic agents that are administered orally and anticonvulsants from their respective protein-binding sites, thereby increasing the clinical effects of these drugs.[29] Therefore, if these drugs are to be used in combination, blood sugar levels, levels of anticonvulsants and the international normalized ratio must be monitored and the dosage of these drugs adjusted. In general, NSAIDs reduce the effectiveness of antihypertensive agents; therefore, blood pressure monitoring is essential when an NSAID is used concomitantly with an antihypertensive agent.

NSAIDs inhibit the clearance of lithium, increasing its effect. If this combination is required, careful monitoring of lithium levels is essential.

The use of NSAIDs and anticoagulants that are administered orally may result in serious bleeding because of the combined inhibition of the extrinsic clotting pathway by the anticoagulant and the NSAID-induced platelet dysfunction. Furthermore, NSAIDs can cause upper GI ulcers in up to 25% of users,[24] and these ulcers may be more likely to bleed in patients taking anticoagulants. The combination of anticoagulants that are administered orally and NSAIDs should be avoided; if it cannot be avoided, misoprostol prophylaxis is necessary.

By inhibiting COX, NSAIDs can, in theory, divert arachidonic acid into the lipoxygenase pathway (Fig. 2), resulting in the increased production of leukotrienes. Since leukotrienes are one of the mediators of bronchospasm, this may be the mechanism of NSAID-induced asthma, which is especially likely to occur in people with a previous history of asthma, nasal polyps or allergic rhinitis. For these patients, if an NSAID cannot be avoided, salsalate may be the safest option because it is a weak COX inhibitor.
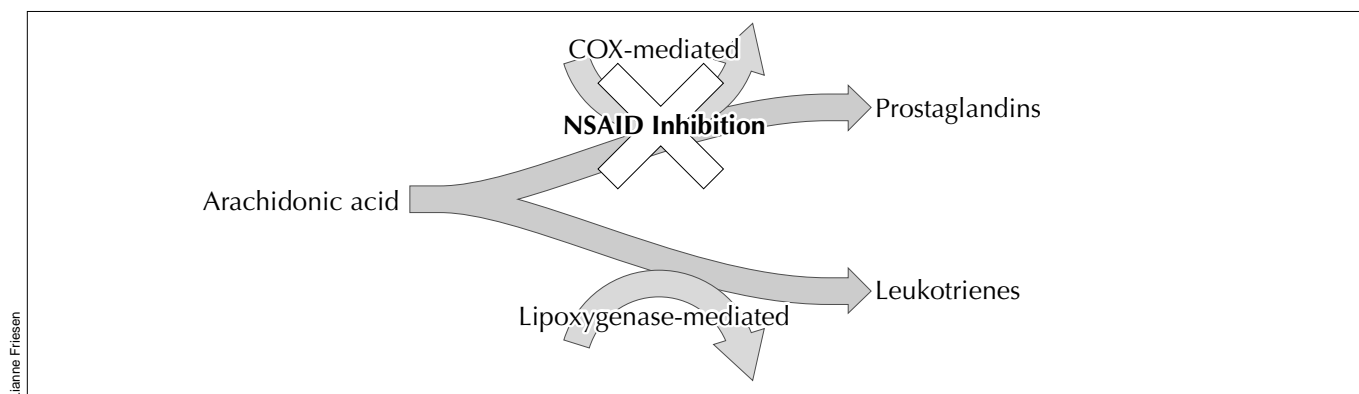
All NSAIDs may cause central nervous system symp-

Fig. 2: Diversion of arachidonic acid into leukotriene production, resulting from NSAID inhibition of COX.

toms, such as headaches, confusion and disorientation; this is particularly common with indomethacin. Some NSAIDs may cause transaminase elevation (more frequent with diclofenac and sulindac). ASA, ibuprofen and sulindac have been reported to cause aseptic meningitis in patients with systemic lupus erythematosus.[30,31] Finally, very infrequent cases of bone marrow suppression have been reported with different NSAIDs, particularly phenylbutazone and indomethacin.[32]

Investigations of the effects of NSAIDs on cartilage metabolism have yielded conflicting results. In some, but not all studies, indomethacin has been shown to accelerate the degradation of cartilage in osteoarthritis of the knee. In one study,[33] tiaprofenic acid was found not to affect the progression of osteoarthritis of the knee. Therefore, the beneficial effect of pain relief of indomethacin in osteoarthritis must be balanced against the possibility of accelerated cartilage damage.

The future of NSAIDs

In 1989, 2 isoforms of COX were identified.[34,35] COX-1 is the constitutive enzyme normally present in platelets, the

> **Key points**
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> - Although the use of vitamins, antioxidants, shark cartilage, glucosamine and chondroitin is increasing, little scientific proof exists to confirm any benefit from these preparations in patients with musculoskeletal pain.
> - In the past few years the injection of hyaluronan into the osteoarthritic knee to restore the viscoelasticity of the synovial fluid has gained acceptance as an alternative to NSAIDs.
> - For specific rheumatic diseases, some NSAIDs appear to be more effective than others; in addition, patient response to NSAIDs may vary considerably.
> - Limited preliminary studies of fatty acids, such as fish oil and evening primrose oil, confirm a modest benefit for these agents in the treatment of various forms of arthritis.
> - Nonpharmacologic therapies, such as massage, manipulation, acupuncture and acupressure, may reduce symptoms temporarily.
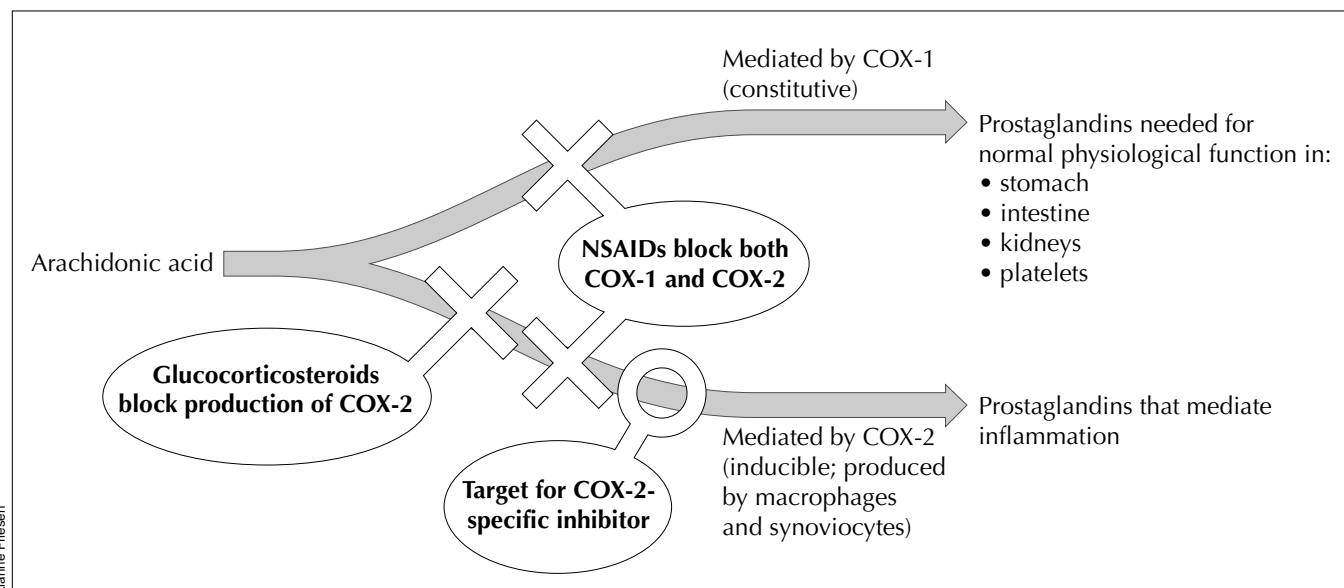
kidneys, the upper GI tract and vascular endothelium that controls the production of prostaglandins required for normal physiologic functions. COX-2, which is induced in inflamed tissue by various cytokines or bacterial lipopolysaccharide (Fig. 3), controls the production of prostaglandins that mediate inflammation in tissues such as the synovium in rheumatoid arthritis and osteoarthritis. Therefore, drugs that specifically inhibit COX-2 should be beneficial in controlling pain and inflammation without interfering with platelet, upper GI tract or endothelial function.

NSAIDs that are currently available are generally nonspecific inhibitors of both COX-1 and COX-2, although etodolac and nabumetone may be slightly more selective inhibitors of COX-2. Celecoxib and rofecoxib, the first of many highly specific COX-2 inhibitors, have recently become available in Canada. This new class of NSAIDs has been found to be as effective as traditional NSAIDs in reducing pain and inflammation, while at the same time they have been shown to have a reduced frequency of side effects, especially clinically significant upper GI lesions.[36–38] If cost is not an issue, 1 of these 2 COX-2-specific agents may be preferable as the first choice of treatment.

Fig. 3: Functions of COX-1 and COX-2 and a target for new NSAIDs.

Alternative and complementary treatments

Nonpharmacologic methods, such as massage, manipulation, acupuncture and acupressure, are often used to treat patients with various rheumatic diseases. In general, these do not cause any harm to patients and may reduce symptoms temporarily. However, spinal manipulation should be avoided in patients with spinal instability, fragility or fusion.

Vitamins, other supplementation and antioxidants have gained increasing popularity among people with musculoskeletal problems. Although no scientific proof exists to confirm any benefit in patients with musculoskeletal pain, in general these do not cause any harm to patients. The use of cartilage components, such as shark cartilage, glucosamine and chondroitin, has also gained popularity in the past few years. There are conflicting reports regarding the efficacy of these therapies.[39–47]

Fatty acids, such as fish oil and evening primrose oil, have been used to treat rheumatic diseases. Limited preliminary studies[48,49] have confirmed the modest benefit of these agents in the treatment of various forms of arthritis.

Antibiotics, such as hydroxychloroquine and sulfasalazine, have been used for many years to treat rheumatic diseases. Recent studies[50] have confirmed the benefits of minocycline in the management of rheumatoid arthritis. Tetracyclines (e.g., minocycline and doxycycline) have been shown to inhibit cartilage-degrading collagenase and metalloproteinase enzymes; their potential use in the treatment of osteoarthritis as structure-modifying drugs is being studied.

In the past few years viscosupplementation has gained acceptance as an alternative to NSAIDs in the treatment of osteoarthritis of the knee. Viscosupplementation is the attempt to restore the viscoelasticity of the synovial fluid by injecting hyaluronan into the osteoarthritic knee.[51] Several preparations of hyaluronan are available commercially. Approximately two-thirds of treated patients have reported satisfactory results for up to 6 months.[51] Of patients treated with hylan G-F 20, 1%–3% have reported transient painful effusion in the injected knee.[51] The use of viscosupplementation is limited by cost, the need for 3 intra-articular injections weekly, its short-term benefit and the lack of a long-term structure-modifying effect in osteoarthritis.

Corticosteroid may be injected locally if symptoms are localized to a single joint or soft tissue and if nonpharmacologic therapy has not been successful.[52]

Treatment for Ms. R

For Ms. R, it is important to recognize that the primary complaint is that of pain caused by osteoarthritis. The history and physical examination revealed no features of a generalized inflammatory arthritis or collagen–vascular disease. Although she has osteoarthritis in her hands, it is not troublesome. Once the problem has been explained, nonpharmacologic treatment should include regular exercise to strengthen the quadriceps muscles and avoidance of activities such as squatting and kneeling. She should take acetaminophen, up to 4 g/d, if necessary. If a satisfactory result is not obtained, viscosupplementation or the addition of an NSAID should be considered. The issues of cost, benefit and possible side effects should be discussed with Ms. R before a traditional NSAID or a COX-2-specific inhibitor is selected. The selected NSAID can be initiated at half the maximum dosage. Depending on the patient's clinical response, the dosage can be titrated up or down. If the selected NSAID has not resulted in satisafctory pain control within 2 weeks, an NSAID of a different class may be tried. The lack of definitive knowledge about glucosamine should be explained to Ms. R and the decision whether to take this compound left to her.

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