Clinical Medicine

Dr Fahim Khan* discusses the recommended non-pharmacological, pharmacological and surgical options for the management of hip and knee osteoarthritis, as well as a number of possible future therapies.

The medical management of osteo arthritis of the hip and knee joints

Osteoarthritis (OA) is the most common musculoskeletal problem in people over the age of 50. Although there is no known cure for OA, treatment designed for the individual patient can reduce pain, maintain and/or improve joint mobility, and limit functional impairment.

In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee. In 1998, the ACR established an *ad hoc* subcommittee to review interim developments in the field and update the recommendations.

The goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy.

The recommended approach to the medical management of hip or knee OA includes nonpharmacologic modalities and drug therapy.

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Patient education

The components of nonpharmacologic therapy are outlined in Table 1. Patient education and, where appropriate, education of the patient's family, friends, or other caregivers are integral parts of the treatment plan for patients with OA. Patients should be encouraged to participate in self-management programmes, such as the Arthritis Foundation Self-Management Programme.

Individuals who participate in these programmes report decreases in joint pain and frequency of arthritis-related physician visits, increases in physical activity, and overall improvement in quality of life.

Another cost-effective nonpharmacologic approach for patients with OA is provision of personalised social support, either directly or by periodic telephone, contact. Studies of the results of monthly telephone calls by trained nonmedical personnel to discuss such issues as joint pain, medications and treatment compliance, drug toxicities, date of next scheduled visit, and barriers to keeping clinic appointments showed moderate-to-large degrees of improvement in pain and functional status without a significant increase in costs.

The physical therapist assesses muscle strength, joint stability and mobility; recommends the use of modalities such as heat (especially useful just prior to exercise); instructs patients in an exercise programme to maintain or improve joint range of motion and periarticular muscle strength; and provides assistive devices, such as canes, crutches, or walkers, to improve ambulation.

Similarly, the occupational therapist can be instrumental in directing the patient in proper joint protection and energy conservation, use of splints and other assistive devices, and improving joint function.

In addition, the input of a vocational guidance counselor may be important to patients who are still actively employed.

In 1995 ACR guidelines also recommended that overweight patients with hip or knee OA lose weight. A randomised open trial of an appetite suppressant and low-calorie diet was completed in 40 overweight patients with knee OA; all patients received instruction in an exercise walking programme.

Patients randomly assigned to the appetite suppressant group lost a mean of 3.9kg over the course of six weeks, and also had significant improvement in their knee OA.

As noted in the 1995 ACR recommendations, proper use of a cane (in the hand contralateral to the affected knee) reduces loading forces on the joint and is associated with a decrease in pain and improvement of function. In addition, patients may benefit from wedged insoles to correct abnormal biomechanics due to varus deformity of the knee.

Medical tapping

Another useful manoeuvre for patients with OA of the knee who have symptomatic patellofemoral compartment involvement is medial taping of the patella.

All of the pharmacological agents discussed in this section should be considered additions to nonpharmacologic measures, such as those described above, which are the cornerstone of OA management and should be maintained throughout the treatment period.

Drug therapy for pain management is most effective when combined with nonpharmacological strategies. (For many patients with OA, the relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen, is comparable with that achievable with an NSAID).

Two recent trails, findings of which were presented at the ACR's 1999 annual meeting, also provide data on the relative efficacy of acetaminophen and NSAIDs in patients with OA. In one study, acetaminophen and ibuprofen were comparably effective in patients with mild to moderate pain, but ibuprofen was statistically superior to acetaminophen for severe pain.

Furthermore, two recent studies of patients with OA demonstrated greater preference for NSAIDs than for acetaminophen, although many patients continue to take acetaminophen. Nevertheless, although a number of patients may fail to obtain adequate relief even with full doses of acetaminophen, this drug merits a trial as an initial therapy, based on its overall cost, efficacy and toxicity profile.

In patients with knee OA with moderate-to-severe pain, and in whom signs of joint inflammation are present, joint aspiration accompanied by intra-articular injection of glucocorticoids or prescription of an NSAID merits consideration as an alternate initial therapeutic approach.

The daily dose of acetaminophen should not exceed 4g. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events.

For those patients who fail to obtain adequate relief with the above measures, alternative or additional pharmacological agents should be considered. The choice should be made after evaluation of risk factors for serious upper gastrointestinal (GI) and renal toxicity. Data from epidemiologic studies show that among persons of age 65 years and over, 20-30 per cent of all hospitalisations and deaths due to peptic ulcer disease were attributable to therapy with NSAIDs.

Furthermore, in the elderly, the risk of a catastrophic GI event in patients taking NSAIDs is dose dependent Risk factors for upper GI bleeding in patients treated with NSAIDs include age > 65 years, history of peptic ulcer disease and, possibly, smoking and alcohol consumption *(Table 2)*.

Risk factors for reversible renal failure in patients with intrinsic renal disease (usually defined as a serum creatinine concentration of > 2.0mg/d) who are treated with NSAIDs include age > 65 years hypertension and/or congestive heart failure, and concomitant use of diuretics and ACE inhibitors.

Additional considerations involved in a practitioner's decision to treat the individual OA patient include existing comorbidities and concomitant therapy, as well as the side effects and costs of specific treatments.

Monotherapy

In individuals with OA of the knee who have mild-to-moderate pain, do not respond to acetaminophen, and do not wish to take systemic therapy, the use of topical analgesics (e.g methylsalicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy.

Capsaicin cream should be applied to the symptomatic joint four times daily; a local burning sensation is common, but rarely leads to discontinuation of therapy.

The options for medical management of OA that has not responded to the above measures in patients who are at increased risk of a serious upper GI adverse event, such as bleeding, perforation, or obstruction, are summarised in Table 3; these include either oral agents or local intra-articular therapy. Two cyclo-oxygenase 2 (COX-2) specific inhibitors, celecoxib and rofecoxib, have been studied in patients with hip or knee OA.

Endoscopic studies have shown that celecoxib and rofecoxib are both associated with an incidence of gastroduodenal ulcers lower than that of comparator NSAIDs and similar to that of placebo. These data suggest an advantageous safety profile compared with that of non-selective NSAIDs, especially for treatment of high-risk patients.

Of further advantage with respect to upper GI bleeding, neither of the COX-2 specific inhibitors has a clinically significant effect on platelet aggregation or bleeding time.

This is a consideration especially in pre and perioperative management of patients with OA (in whom nonselective NSAIDs have traditionally been discontinued as long as two weeks prior to surgery), as well as for patients taking warfarin sodium.

Accordingly, these patients appear preferable to currently available nonselective NSAIDs for use in patients at risk of upper GI complications. Additionally, at doses recommended for treatment of OA, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of dyspepsia and other GI side effects, than comparator nonselective NSAIDs. Like nonselective NSAIDs, however, COX-2 specific inhibitors can cause renal toxicity.

An alternative to the use of COX-2 specific inhibitors is the use of nonselective NSAIDs with gastro-protective agents, as described in the 1995 ACR recommendations and endorsed by the American College of Gastroenterology.

If nonselective NSAIDs are used, they should be started in low, analgesic doses and increased to full anti-inflammatory doses only if lower doses do not provide adequate symptomatic relief. In the patient who is at increased risk of a serious upper GI adverse event, gastroprotective agents should be used even if nonselective NSAIDs are given at low dosage.

In a study of 8,843 patients with RA, 200 micrograms misoprostol four times a day reduced the incidence of complicated ulcers, including those with perforation, bleeding, and obstruction, by 51 per cent.

In a 12-week, randomised, double-blind, placebo-controlled endoscopy study, 200 micrograms misoprostol three times a day had comparable efficacy in preventing both gastric and duodenal ulcers; however 200 micrograms misoprostol twice a day conferred significantly less protection from gastric ulcers. Nonetheless, side effects, particularly diarrhoea, and flatulence, may occur with this agent, in a dose dependent manner.

Not as effective

Alternative approaches to prophylaxis with misoprostol include the use of high-dose famotideine or omeprazole, both of which have been shown to be effective in treating and preventing NSAID gastropathy in carefully conducted endoscopy studies. H_2 blockers in usual doses, however, have not been found to be as effective as misoprostol. Either 20mg/day or 40mg/day omeprazole was as effective as misoprostol 200 micrograms twice a day in the treatment of existing ulcers and was better tolerated and associated with a lower rate of relapse. Proton pump inhibitors, however, have not been approved by the FDA for use in prophylaxis, although they are being widely used for that purpose.

Risk of bleeding

In addition to their side effects on the GI mucosa, nonselective NSAIDs inhibit platelet aggregation, further increasing the risk of GI bleeding. Nonacetylated salicylates (e.g. choline magnesium trisalicylate, salsalate) are not accompanied by the anti-platelet effects or renal toxicity associated with nonselective NSAIDs, and can also be considered in management of high-risk patient; however, ototoxicity and central nervous system toxicity at clinically efficacious doses may limit their use.

An alternative approach to the use of oral agents in the palliation of joint pain is the use of intra-articular therapy such as hyaluronan (hyaluronic acid) or glucocorticoids. Two preparations of intra-articular hyaluronan have been approved by the FDA for the treatment of knee OA patients who have not responded to a programme of nonpharmacological therapy and acetaminophen. To date, differences in clinical efficacy between these preparations as a function of molecular weight have not been demonstrated. Because the duration of benefit reported for these agents exceeds their synovial half-life, their mechanisms of action are unclear; proposed mechanisms include inhibition of inflammatory mediators such as cytokines and prostaglandins, stimulation of cartilage matrix synthesis and inhibition of cartilage degradation, etc.

Pain relief

In clinical trials of intra-articular hyaluronan preparations, pain relief among those who completed the study was significantly greater than that seen after intra-articular injection of placebo and comparable with that seen with oral NSAIDs.

In addition, pain relief among those who completed the study was comparable with or greater than that with intra-articular glucocorticoids. Although pain relief is achieved more slowly with hyaluronan injections than with intra-articular glucocorticoid injections, the effect may last considerably longer with hyaluronan injection.

Intra-articular hyaluronan injections may be especially advantageous in patients in whom nonselective NSAIDs and COX-2 specific inhibitors are contraindicated, or in whom they have been associated either with a lack of efficacy or with adverse events.

Limited data are available concerning the effectiveness of multiple courses of intra-articular hyaluronan therapy. Transient mild-to-moderate pain at the injection site may occur; occasionally, mild-to-marked increases in joint pain and swelling have been noted following hyaluronan injection.

Intra-articular glucocorticoid injections are of value in the treatment of acute knee pain in patients with OA and may be particularly beneficial inpatients who have signs of local inflammation with a joint effusion. When joints are painful and swollen, aspiration of fluid followed by intra-articular injection of a glucocorticoid preparation (e.g. up to 40mg triamcinolone hexacetonide) is an effective short term method of decreasing pain and increasing quadriceps strength. Injection can be used as monotherapy in selected patients or as an adjunct to systemic therapy with an analgesic.

Joints should be aspirated/injected using aseptic technique, and the fluid should be sent for a cell count. Gram stain and culture should be performed if infection is suspected. Some patients may experience a mild flare of synovitis due to a reaction to the crystalline steroid suspensions; however, these post injection flares are temporary and can be treated with analgesics and cold compresses. The risk of introducing infection into an OA joint is exceedingly low if standard aseptic technique is used.

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that also inhibits reuptake of norepinephrine and serotonin. It has been approved by the FDA for the treatment of moderate-to-severe pain and can be considered for use in patients who have contraindications to COX-2 specific inhibitors and nonselective NSAIDs, including impaired renal function or in patients who have not responded to previous oral therapy.

The efficacy of tramadol has been found to be comparable with that of ibuprofen in patients with hip and knee OA. Mean effective daily doses of tramadol have generally been in the range of 200-300mg, given in four divided doses.

Side effects are common and include nausea, constipation, and drowsiness. Despite its opioid pharmacology, a comprehensive surveillance programme has failed to demonstrate significant abuse and tramadol remains an unscheduled agent.

Opioid therapy

Patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain may be considered candidates for more potent opioid therapy. In one study, the combination of codeine plus acetaminophen was shown to provide significantly better analgesia than acetaminophen alone in patients with hip OA, although one-third of patients receiving the combination discontinued therapy due to nausea, vomiting, dizziness or constipation. In a short-term study, of acute pain in patients with hip or knee OA, no difference in analgesic efficacy was demonstrated between combinations of acetaminophen with either dextropopoxyphene or codeine; however, the combination with detropropoxyphene was significantly better tolerated. Tolerance, dependence and adverse effects, including respiratory depression and constipation may occur with opioid usage.

Table 1.

Non-drug therapy for patients with osteoarthritis

Patient education
Self-management programmes
(e.g. Arthritis Foundation Self-Management Programmes)
Personalised social support through telephone contact
Weight loss (if overweight)
Aerobic exercise programmes
Physical therapy range-of-motion exercises
Muscle-strengthening exercises
Assistive devices for ambulation
Patellar tapping
Lateral-wedged insoles (for genu varum)
Bracing
Occupational therapy
Joint protection and energy conservation
Assistive devices for activities of daily living

Dose of aspirin

Although the efficacy of therapy with combinations of the above pharmacological agents has not been established in controlled clinical trials, in general, it is reasonable to use the recommended agents in combination in an individual patient. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardio protective dose of aspirin (81-325mg/day) with other NSAIDs.

Even these low doses of aspirin, however, will increase the risk of upper GI bleeding in patients taking NSAIDs. In this regard, it should be noted that the incidence of endoscopically identified ulcers in patients taking a COX-2 specific inhibitor and a cardioprotective dose of aspirin was lower than that in comparator groups taking nonselective NSAIDs with or without concomitant low dose aspirin.

In OA patients who are already taking an NSAID, but who have not incorporated relevant nonpharmacologic measures (e.g. an exercise programme, weight loss programme, adherence to principles of joint protection) into their treatment programme, such measure should be implemented. This may permit reduction of the dosage of NSAID or replacement of the NSAID with acetaminophen.

In all patients whose symptoms are well controlled, attempts should be made periodically to reduce the dosage of NSAID and/or analgesic agents and to determine whether it is possible to use such agents on an as-needed basis, rather than in a fixed dosing regimen.

While the 1995 ACR guidelines recommended that tidal irrigation (TI), should be considered for those patients with knee OA that did not respond satisfactorily to nonpharmacologic and pharmacologic measures, it was cautioned that information did not exist concerning the magnitude of the placebo response to this procedure. Although some data suggest that TI may be efficacious in some patients, the subcommittee believes that a statement concerning the role for this modality should await further study.

It should be noted that therapy for OA of the hip is similar to treatment of OA of the knee, except for a few minor differences. Intra-articular hyaluronan therapy is not approved for hip OA and there are no published studies regarding its efficacy in patients with hip OA. Topical agents have not been studied in hip OA, and their efficacy is questionable because of the depth of that joint.

Intra-articular glucocorticoid injections have not been studied in patients with hip OA but are used occasionally and may be efficacious. Injections performed without fluoroscopic guidance should be administered only by those experienced in this approach. Modalities of physical therapy for patients with hip OA differ from those used in patients with OA of the knee. Consultation with a physical therapist should be considered as part of the overall management.

Patients with severe symptomatic OA who have pain that has failed to respond to medical therapy and who have progressive limitation in ADLs should be referred to an orthopaedic surgeon for evaluation.

In appropriately selected patients who are not yet candidates for total joint arthroplasty, osteotomy may provide pain relief and prevent progression of disease.

Total joint arthroplasty provides marked pain relief and functional improvement in the vast majority of patients with OA, and has been shown to be cost effective in selected patients. Indications for total hip replacement include "radiographic evidence of joint damage and moderate to severe persistent pain or disability, or both, that is not substantially relieved by an extended course of nonsurgical management".

While there are no published evidence-based indications for total knee replacement, outcomes depend upon the timing of the surgery, the experience of the surgeon and the hospital and the patient's preoperative medical status, peri- and postoperative management, and rehabilitation.

Considerations

While a number of studies support the efficacy of both glucosamine and chondroitin sulfate for palliation of joint pain in patients with knee OA, the subcommittee believes that it is premature to make specific recommendations about their use at this time because of methodological considerations, including lack of standardised case definitions and standardised outcome assessments, as well as insufficient information about study design in a number of these published reports.

A pivotal clinical trial is being planned which should help define the role of these agents alone, and in combination, in the treatment of patients with knee OA.

Pulsed fields

In addition, currently existing data are insufficient or inadequate to permit the subcommttee to make definitive recommendations about the use of devices, such as pulsed electromagnetic fields and lasers. Further research is needed on vitamin deficiencies which have been suggested as possible causes of (or aggravating factors in) OA, before dietary supplementation can be recommended for prevention or treatment of this disease.

Similarly, the value, if any, of other nutritional supplements, including supraphysiologic doses of anti-oxidant vitamins, remains to be determined.

In addition, therapeutic approaches such as acupuncture are difficult to evaluate and recommend because of large placebo effects of invasive procedures and the lack of adequate sham-controlled studies. An ongoing, pivotal, randomised, sham-controlled trial of acupuncture is under way; this trial should help define acupuncture's role in the treatment of patients with knee OA.

Prevention

The 1995 ACR recommendations briefly mentioned preliminary studies of disease-modifying OA drugs (DMOADs), drug whose action is not aimed principally at the control of symptoms, but instead at the prevention of structural damage in joints already affected by OA or at the progression of structural damage in joints already affected by OA.

Table 2.

Risk Factors for Upper GI Adverse Events

Age > 65 years
Comorbid medical conditions
Oral glucocorticoids
History of peptic ulcer disease
History of upper GI bleed
Anticoagulants

For the most part, such approaches have been aimed at inhibiting the breakdown, of articular cartilage by matrix metalloproteinases, or at stimulating repair activity by chondrocytes. Although a number of agents are under study, including matrix metalloproteinase inhibitors and growth factors, no agent has been shown to have a DMOAD effect in humans, and none are available for this indication.

In addition to therapeutic agents targeted toward prevention, retardation, or reversal of cartilage breakdown in OA, significant advances, such as autologous chondrocyte transplantation, cartilage repair using mesenchymal stem call, and autologous osteochondral plugs are being investigated for repair of focal chondral defects.

These procedures are not currently indicated in the treatment of patients with OA.

Given the advances in therapy which can be anticipated for patients with OA, it is likely that the current recommendations will change as new knowledge of the disease unfolds and new therapies become available.

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Table 3.

Drug therapy for patients with osteoarthritis

Oral:
Acetaminophen
COX-2 specific inhibitor
Nonselective NSAID plus misoprostol or a proton pump inhibitor
Nonacetylated salicylate
Other pure analgesics
Tramadol
Opioids
Intra-articular glucocorticoids
Hyaluronan

Topical:
Capsiacin
Methylsalicylate

* *The choice of agent(s) should be individualised for each patient as noted in the text.*
***Misoprostol and proton pump inhibitors are recommended in patients who are at increased risk of upper gastrointestinal adverse events.*