Osteoarthritis - Beyond Pain Relief

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Oncologists have taught us a lot. We have learnt not to lose hope and to keep on working towards the benefit of patients. We have seen the progress in the management of Cancers - from no care, to palliative care, to definitive treatment, to cure. One of the earliest treatments described for Cancer Breast was cautery with the help of a burning branch of wood. This crude palliative care gave rise to more refined palliative care including treatments like lumpectomy, pain relief. Definitive care came in the form of more advanced radical surgery and radiotherapy. However despite impressive gains all treatments failed in late and widespread disease. Survival curves for different malignancies have shown that if malignancy is treated at Stage 1 the prognosis is much better than if treated late in stage 4. A simple lumpectomy in Stage I Ca breast may cure the disease where as complex radical mastectomy may not be sufficient for advanced disease. Now the emphasis is to screen for cancer and detect and treat it before it becomes a real disease. Currently screening for Ca Cervix saves 5000 deaths in UK whereas only about 1000 die every year.

What have the Rheumatologists picked up from the Oncologists? - A strategy for the management of RA. This strategical shift from palliative therapy to definitive therapy includes (i) Use of Combination Disease Modifying therapy, (ii) Early treatment, and (iii) Treat to Target. The target in Rheumatoid Arthritis is set to “Remission or very low disease activity” Using this target it has been possible to produce 65% Remission Rates using standard Disease Modifying Anti Rheumatic drugs in the TICORA Trial (Grigor et al 2004). With Anti TNF drugs 40% Remission is seen in MTX Resistant patients. Rituximab produces another 15% remission in Anti TNF resistant patients. A Combination of Standard DMARD + Anti TNF in “Early” patients may produce up to 90% remission.

Have we learnt anything for Osteoarthritis from experiences in RA and Malignancy?

OSTEOARTHRITIS - MAJOR UNMET MEDICAL NEED OF THE COUNTRY.

OA inflicts about 4-6 crore (40-60 million) Indians. It afflicts about 4% of population and 10% of adult population. The importance of Osteoarthritis can be gauged by comparing this with the prevalence of Rheumatoid Arthritis which is only 0.5-0.7% (2-3 million) of adult population. Other immunological causes of arthritis and musculoskeletal pain are even rarer. Osteoarthritis is third commonest cause of DISABILITY. Osteoarthritis is the Future of Rheumatology.

MANAGEMENT OF OSTEOARTHRITIS

Currently accepted goal of Management of Osteoarthritis is “Pain relief” with the use of Paracetamol. It is recommended that NSAIDs should be used only when paracetamol does not work and should be used for the least possible time. All NSAIDs have a black box warning that they are harmful. If there is inadequate pain relief then opioids may be added to the treatment. The use of all other medications available for treatment of Osteoarthritis is disparaged upon. The other form of therapy that is acceptable is a total knee replacement surgery (TKR), which does take care of the pain in a bulk of the patients but is not suited for the Indian style of living of squatting and sitting on the floor. It is expensive and out of reach of most patients in the country. If 0.25% patients of OA need TKR then total burden to the tax payer will be 1 lac crore or more. Pain relief by paracetamol or TKR can be best described as palliative therapy.
Since pain relief and consequent improvement in function is the current target it would be worthwhile to see the effect of various therapies on Pain relief. Effect sizes for Pain relief with different pharmacological treatments have been compared in a recent Meta-analysis (Zhang et al, 2007). IA corticosteroid, Glucosamine sulphate, Chondroitin sulphate and COX 2 Inhibitors have the best effects. The unmodified Figure 3 of the manuscript by Zhang et al, has been reproduced here as Figure 1 below:

However the best effect size amongst of all kinds of treatment is summarized in the Table 1 below:

Thus it is clear that none of the OA Therapies are very effective alone. Better results may be obtained with the use of combinations. Secondly some disease modification seems possible.

**GENERAL SCHEME OF PATHOGENESIS**

Previously it was thought that Osteoarthritis is a pure degenerative disease of old age. However, now the role of Inflammation in Osteoarthritis is being realized. It is now considered that Inflammation is a key mediator in the pathogenesis of OA. Our experience is that 25-30% patients with Osteoarthritis knees have Clinical inflammation at time of presentation. On evaluation 80-90% of symptomatic knees OA have synovitis seen on MRI. This has bearing on management. The Moral of the story is that Non Steroidals have better efficacy than paracetamol and IA steroids are one of the best and most effective treatments for Osteoarthritis pain. Figure 2 shows a simplified scheme of pathogenesis of OA. IL1 is the key mediator of inflammation in OA. The pathways that lead to production of IL1 in Osteoarthritis are under research. There is a need for treatments that target inflammation for management of Osteoarthritis.

**TREATMENTS THAT SPECIFICALLY TARGET INFLAMMATION**

Pharmacological therapies that specifically target inflammation and have been tried in Osteoarthritis are

1. Non Steroidal Anti-inflammatory drugs.
2. IA steroid
3. IA Anti TNF antibody - well tolerated but no significant relief.
4. IA IL1 Receptor Antagonist
5. Colchicine
6. Doxycycline has been shown to have disease modifying properties without any effect on pain.

Other OA Therapies that were started with other reasons have also been reported to reduce Inflammation. These include

1. Glucosamine sulphate
2. Chondroitin sulphate
3. Inj. Hyaluronan IA
4. Diacerein (believed to be IL1 antagonist).

Of the various therapies that target inflammation effects of NSAIDs and IA Corticosteroids has already been commented upon. Anti TNF antibody therapy has been studied in one trial and has shown good tolerability but no significant efficacy. It is not expected that a single shot of Anti TNF agent or anti IL1 agent will produce significant effects because of short duration of action.

IL-1 RECEPTOR ANTAGONIST – ANAKINRA

In a study to assess the dose of Anakinra to be administered, the investigators gave six doses from 0.05 mg up to 150 mg, intra-articular. There was no Placebo control, but the study was double-blinded regarding the dose administered. Significant improvement was seen until Month 3 in patients who received 150 mg (n=13). Pain improved by -20.4 ± 23.3 mm (p = 0.008) and WOMAC global score by -19.5 ± 20.1 (p = 0.005) (Chevalier et al 2005). When Anakinra was used as a single Intra-articular injection of 50-mg or 150-mg it was well tolerated. However it was not associated with improvements in OA symptoms at 4 weeks compared with placebo (Chevalier et al 2009) but showed early analgesic activity at 150 mg dose.

COLCHICINE

Colchicine was used by us in with the belief that colchicine will prevent inflammation in patients with crystals. Osteoarthritis is frequently associated with Chondrocalcinosis. It has been shown that 30-70% patients with OA have Synovial Fluid CPPD or BCP crystals in their joint fluid and cartilage. Crystals are associated with more severe OA, with more severe joint damage and with inflammation. Since colchicine is known to be effective in Crystal induced arthritis it was used in setting of OA.

Colchicine was found effective in patients with OA with CPPD crystals in Joint Fluid in an open placebo controlled trial. In a subsequent double blind placebo controlled RCT it was shown to be effective in patients with OA with inflammation of knee joint irrespective of whether crystals were present or not. In a third trial which was again double blind placebo controlled RCT it was shown to be effective in patients with OA irrespective of whether inflammation was present or not. Two double blind trials from Iran and Agra India have shown benefit using Colchicine. Colchicine seems to be targeting the pathway between cell stimulation to release and activation of IL1.

TARGET FOR TREATMENT OF OSTEOARTHRITIS

Palliative Targets: Research in Osteoarthritis has suffered from lack of appropriate Targets for the treatment. The major target so far has been pain relief and consequent improvement in function or Palliation. In the 1980’s composite measures of pain relief and improvement in function came up in form of WOMAC scores and Lesquene index. Most treatments have been assessed on these targets. Oncology studies have shown that treatment targeting Palliation ultimately fails.

Definitive Treatment Targets: Less progression of Joint Space Narrowing seen on serial radiographs has been used as the definitive disease target. Radiological assessments have been standardized for this purpose however many investigators still criticize the procedure since sometimes posture affects the quantitation of joint space narrowing. A better method to quantitate cartilage is required for setting the target for treatment. Besides Osteoarthritis is a disease that involves all parts of the joint and not just the cartilage. Hence a comprehensive assessment of joint is required. MRI has been used for the purpose and comprehensive scores have been developed. Two commonly used scoring systems are WORMS and BLOKS scoring systems.

CAN A STRATEGY OF USING MRI TO STUDY RESPONSE WORK?

Wildi et al 2011 studied Disease Modification using Chondroitin sulphate by MRI. They found a decrease in Cartilage loss as early as 6 months and lasting for a year. They also showed that there was a reduction in Bone Marrow lesions (BML’s) at one year. BML’s are considered important features of Osteoarthritis seen on MRI. However there was no effect on disease symptoms. It appears that a MRI based target is now available that can be used to measure response to treatment in Osteoarthritis.

EARLY DIAGNOSIS OF OSTEOARTHRITIS

It has been seen that treatment at an early stage has made a big difference in the management of cancers and even in Rheumatoid Arthritis. Hence an early diagnosis of Osteoarthritis is required. But is an early diagnosis possible? It seems that it is now possible.

A MRI definition of knee Osteoarthritis has been developed, which includes the following features:

1. Cartilage defects. (Best seen on Intermediate weighted FSE Fat suppressed)
2. Bone Marrow lesions (Best seen on Proton Density weighted, FSE, Fat suppressed sequences)
3. Meniscal tears (Best seen on Intermediate weighted Fat suppressed sequences)
4. Osteophytes (Best seen on T1 Weighted images)

It is also possible to see for alterations in proteoglycan content and water content of Cartilage. Intrachondral alteration of signals reflecting changes to collagen or edema may herald diagnosis of Preosteoarthritis. This is possible by
using dGEMERIC MRI, Na MRI, and T1p MRI. However their utility is yet to be established. Using MRI criteria of Diagnosis it has been possible to diagnose OA very early. In patients with infrequent knee pain it has been shown that patients may not have radiographic changes but may have MRI changes of Osteoarthritis. This can be classified as Pre-radiographic Osteoarthritis. These Pre radiographic MRI changes may predict development of OA symptoms in patients with infrequent knee pain (Javaid et al 2010). It has also been shown that a fluctuation in knee pain in Preradiographic OA occurs with changes in BML size. In another study MRI demonstrated presence of changes suggestive of Osteoarthritis in about 13% of adult women without knee pain (Guymer et al 2007). This provides a possibility of diagnosing preclinical and pre-radiographic osteoarthritis. I am tempted to classify Osteoarthritis into the following stages:

STAGES OF DIAGNOSIS OF OSTEOARTHRITIS
1. Symptomatic Osteoarthritis
2. Radiological Osteoarthritis
3. Clinical Pre-radiological Osteoarthritis
4. Preclinical, Pre-radiographic Osteoarthritis

WILL EARLY THERAPY HELP?

Even if an early diagnosis has been made, is there evidence that early treatment would help? It has been shown that early use of Glucosamine, Chondroitin etc reduce levels cartilage turnover markers. It is also known that existing joint damage is a predictor of progression. Hence if initial joint damage is prevented it may not progress. We all know that late disease, when joint damage has already occurred, is not likely to respond to medical treatment. Just as lumpectomy may suffice in early Breast Cancer existing therapies may suffice for prevention and treatment of early and very early osteoarthritis.

IS THIS THE FUTURE?

The future is likely to be very exciting. As new pathways are being detected new treatment options will appear. But what will make a big difference is a scenario where a high risk group will be identified; preclinical and preradiographic osteoarthritis will be diagnosed and patients offered preventive/curative treatment. A follow up or monitoring on Serial MRI will be enlighten us about the utility of the approach. Such a high risk group may include individuals with following characteristics (i) Obesity, (ii) Age more than 30-40, (iii) Female Sex, (iv) Past knee joint injury, and (v) Family history.

QUESTIONS THAT NEED TO BE ANSWERED

This exciting era will be ushered in once the following questions are answered by good and reproducible studies.

1. Does this early preclinical-pre-radiographic diagnosis with MRI correlate with OA later on?
2. Will treatment at this stage make a difference to occurrence of symptomatic OA?
3. Will treatment at this stage prevent progression of Osteoarthritis?
4. Will treatment at this stage prevent deformities and joint replacement surgeries?
5. Will treatment at this stage cure OA?

In summary “What have we learnt from the Oncologists?” - A totally new Approach.

REFERENCES