Intra-Articular Steroids in ‘Treat-to-Target’ Therapy in Early Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory polyarticular autoimmune disease affecting 0.4-1% of general population. It causes cartilage destruction and bony erosions in synovial joints. Activation of T lymphocytes by unknown antigens, stimulates monocytes, macrophages and synovial fibroblasts to produce cytokines, interleukin 1, 6 and TNF α in the synovial fluid. This triggers the inflammatory cascade by stimulation of synovial fibroblasts, osteoclasts and chondrocytes that release matrix metalloproteases (MMP). These MMP’s and the neutrophilic enzymes namely elastases and proteases degrade the cartilage causing joint destruction. Apart from this the activated T cells also cause an osteoprotegerin ligand mediated osteoclastogenesis and consequent bone loss.

In earlier stages of the disease, there is demonstrable presence of inflammatory markers in blood as well as the synovium. At this stage, there is joint pain and swelling, significant morning stiffness without much radiographic abnormalities that can be picked up on the X-rays. Although musculoskeletal ultrasound (MSU) and MRI of the small joints of hands can pick up early RA, its cost in the developing world prevents its routine use for the diagnosis of early RA. In the developed nations, there are early arthritis clinics run by the doctors as well as qualified trained nurses. In these clinics, there is an opportunity for early diagnosis by MSU where joint inflammation is picked up even before it clinically manifests as synovitis. Hence there is an opportunity for early aggressive therapy. With an increased awareness amongst patients and doctors in the last decade in developing countries like ours, there has been a decrease in the number of patients who used to present directly with deformities. Still, there are a large number of patients even in the 21st century who do present with deformities at the first visit to a rheumatologist for treatment.

The treatment of RA has also undergone revolution and the old “pyramidal approach” has topsiturved to reverse pyramid; the present concept being ‘treat-to-target’ and achieve early remission/low disease activity scores. DMARDS and Biologics have revolutionised the therapy in RA. DMARDS are slow in action and will take 6-8 weeks to start their efficacy. While Biologic response modifiers (BRM) due to high cost are not yet within the financial scope of common man. Only those with reimbursement facilities, the cost being borne by the employer or medical insurance covering biologic cost are able to receive its benefit. As a result of which the time tested corticosteroids are still the wonder drugs which are recommended in the treatment of RA to be used judiciously and rationally. Oral steroids cause a lot of well-known side effects like diabetes mellitus, hypertension, premature cataracts, osteoporosis or Cushing’s syndrome. Hence their use should be curbed for a shorter duration with the least possible dose. Therefore intra-articular steroid (IAS) injections have been a safer option in the treatment of inflamed joints in RA. The various steroids that have been used intra-articularly are betamethasone, triamcinolone and methylprednisolone. IAS impair the ability of monocytes
to release TNF α and suppress levels of other mediators like IL-1,6 and 8.2,3 IAS cause reduction in inflammatory markers like CRP and ESR that starts within few hours and lasts for months.4 They can also induce remission in patients with extra-articular manifestations.4 In a study reported from Norway by Haugeberg G et al, IAS offers protection against periarticular bone loss in inflamed joints in RA. This data also emphasises the importance of suppressing inflammation in patients with active RA to maintain bone health.5

The CIMESTRA study group have evaluated the short and long-term efficacy of IAS injections with betamethasone as part of ‘treat-to-target’ strategy in early RA. It was found that there was a rapid, effective and long-lasting inflammatory control with betamethasone.6 Although, IAS are considered safe, they cause decrease in serum cortisol within 24-48 hours. Recovery usually takes 1-4 weeks and sometimes longer depending on the dose, the type of steroid and the number of injections.4 In a poster presented by Singh BK et al during IRACON 2012 at Ahmedabad, a transient rise in blood glucose levels after IAS in patients of RA who were non-diabetic was reported on day 1 in 60% patients.7 While considering the utility of any therapy, it is necessary to assess its cost-effectiveness. Very few trials have studied this aspect of IAS injections. In a study reported by Chavez-Chiang NR from the USA, the investigators have compared the conventional syringe technique and the mechanical syringe technique and found that the mechanical syringe technique not only was better as far as the efficacy is concerned but also caused 23% reduction in cost/patient/year for a patient treated in physician office; 24% reduction in cost/patient/year for a hospital outpatient and 51% reduction in cost/responder/year.8

Dennis E et al,9 from France have given the following recommendations based on clinical practise based data from literature and expert opinion: 1. Bolus IV steroids should be reserved for special situations like vasculitis, ILD, etc. 2. Triamcinolone hexacetonide is the preferred glucocorticoid for intra-articular therapy and the injected joint should be rested for at least 24 hours after the IAS injection. 3. When needed orally, an agent with short half-life, once daily dosage should be preferred and while discontinuing the oral steroids, the patient and the physician should be informed about the possible risk of adrenal insufficiency.

In a study reported from Brazil, 96 patients of RA undergoing IAS injection in peripheral joints were evaluated for their accuracy. The patients were evaluated clinically at baseline, 1 week and 4 weeks. A statistically significant improvement occurred in them in Visual Analogue Scale (VAS) for pain, oedema and morning stiffness. The joints like shoulder, elbow, wrist, MCP joints, knee and ankle showed 82,100,97,97,100 and 77% accuracy when injected blindly.10

In the present issue of JAPI, triamcinolone acetate has been studied by Nitin Menon et al as the IAS in RA. The patients receiving DMARDS alone (control group) were compared with patients receiving DMARDS plus IAS (study group). The study group showed significant reductions in DAS 28 scores, more patients in the study group achieved ACR 20/50/70 criteria at the end of 3 months. Also ESR, tender joint count and swollen joint count, early morning stiffness improved markedly in the study group. The authors have concluded by saying that this study results show that DMARDS plus IAS would be an effective option to the expensive biologics in treatment of early RA.11 They have also recommended that more studies comparing Biologics with DMARDS plus IAS should be done to support their conclusions.

It was interesting to read the OPERA study results recently published in Annals of Rheumatic Diseases April 2014. This study was conducted in Denmark to evaluate whether Adalimumab added to methotrexate and intra-articular triamcinolone as first-line therapy in early RA increased the frequency of low disease activity (DAS28CRP<3.2) at 12 months. It did not increase the proportion of patients who reached the DAS28CRP<3.2 treatment target; however it did improve DAS28CRP, remission rates, function and quality of life in DMARD-naive early RA patients.12 So IAS with DMARDS is definitely useful in the aggressive management of early RA. While injecting the same joint, not more than 3 injections should be given in 1 year.

References


