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TREATMENT OF ANKYLOSING SPONDYLITIS WITH SPECIAL REFERENCE TO BIOLOGICS: SINGLE CENTRE EXPERIENCE

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Abstract:
Ankylosing Spondylitis (AS) is one of the most common inflammatory rheumatic disorders. Its pathogenesis is poorly understood but HLA-B 27molecule,immune cells and cytokines are all thought to play a role. The detection of sacroilitis by imaging in presence of clinical manifestation is diagnostic. Non-steroidal anti-inflammatory agents are the first line of drugs and they effectively relieve symptoms. NSAIDS refractory patients are treated with second line drugs e.g. corticosteroid, DMARDS and pamidronate. Recently biologic therapies using Infliximab help target underlying inflammatory process in AS and may alter the disease process along with significant symptomatic improvement.

Introduction :

Ankylosing Spondylitis (AS) is a chronic systemic inflammatory rheumatic disease,[1] primarily affecting the axial skeleton of which sacroilitis is the hallmark. The disease pathogenesis is immune mediated as evident by raised IgA and close relationship with HLA B27[2]. Immunologically there is interaction between class I HLA molecule B27 and T lymphocytes. Tumor necrosis factor (TNF-α) has been identified as key regulatory cytokine[2].

The age of onset is second or third decade of life[2] and males are affected two to three times more than females[3]. In our Rheumatology Clinic (IPGMER, Kolkata) the male-female ratio is 3:1. The risk factors for the disease are presence of HLA B27, male sex, positive family history,[4] etc. Of them HLA B27 is most important as there is almost sixteen times increased chance of developing the disease amongst HLA B27 positive relatives. HLA B27 is present in almost 90%-95% cases[5] (about 73% in our rheumatology clinic).

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The clinical features are insidious onset, dull pain felt in lower lumber region, associated with morning stiffness lasting for few hours, there may be asymmetric arthritis of other joints mainly of lower limbs. Neck pain and stiffness is present in advanced cases. Physical findings include loss of spinal flexion, extension, lumber lordosis, diminished chest expansion, and exaggerated thoracic kyphosis.

Increased CRP, ESR have limited value in determining disease activity[6]. CT and MRI are helpful in early detection of sacroilitis[7] The assessment of disease activity is difficult because the laboratory indicators of inflammatory arthritis neither reflects clinical nor radiological progression[8] and for this reasons the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) a self administered instrument has been developed.

Disease modifying antirheumatic drugs (DMARDS) – e.g. Sulfasalazine, methotrexate, corticosteroids are used in NSAIDS intolerance, patients refractory to NSAIDS, advanced and severe cases. Recently introduced biological agents (e.g. - TNF-α blockers) have demonstrated good efficacy in the treatment and also in presenting disability in patients with severe AS. The biological agents are chimeric mono-

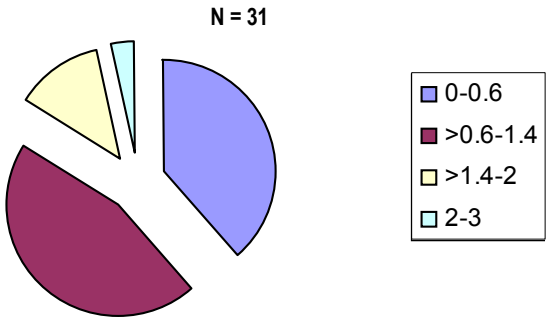
clonal antibody – Infliximab and the 75 KDa IgG receptor fusion protein Etanercept. Several open label and randomized control studies have evaluated the efficacy of Infliximab in patients with AS.

Open label pilot study conducted by Braun, Brandt et al showed that Infliximab was very effective[9] in controlling disease activity in patients with severe AS. 11 patients suffering from AS for a median period of 5 years received three infusions of Infliximab at the dose of 5mg/kg at weeks 0, 2nd and 6th. The positive effects occurred as early as one day after the infusion and lasted until week 12th and also with continued clinical benefit.

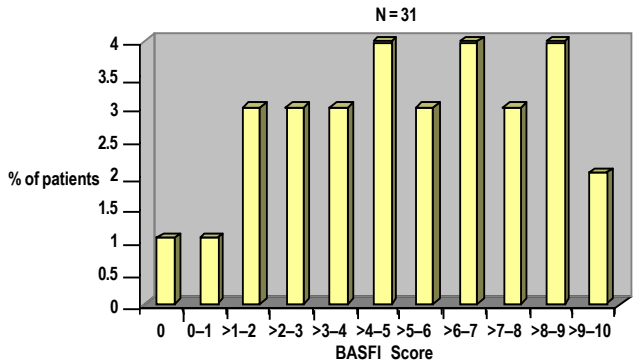
One randomized control trial – German multicentric study[10]; 70 patients with active AS were randomly allocated to receive either Infliximab (5mg/kg) or placebo at week 0, 2 and 6. Clinical and laboratory assessment was done at week 12 and 53% patients in Infliximab group had a greater than 50% improvement as compared to 9% in the placebo group.

In our Rheumatology clinic at IPGMER, Kolkata we have evaluated 31 patients of AS (23 males and 8 females).

NSAIDS *:* All 31 patients were treated with celecoxib 200 mg twice daily for 4 weeks followed by 200 mg daily at bed time for 12 wks. Around 20% patients had minor GI symptoms such as dyspepsia,



HAQ Distribution in AS at rheumatology clinic, IPGMER, kolkata



BASFI distribution in AS at rheumatology clinic, IPGMER, kolkata

epigastric pain, nausea, diarrhoea. Life threatening complications in the form of perforation, ulceration and bleeding did not occur. 7 patients did not respond to NSAIDS.

Corticosteroids : NSAID refractory cases were treated with Injection Methyl prednisolone 1 G IV on three consecutive days. Early morning stiffness, pain improved within one week (BASDAI Score) whereas improvement of overall spinal movement reached its maximum at week four after pulse therapy.

Sulphasalazine : Out of 31 patients, 13 patients (41%) had peripheral arthritis in addition to axial involvement. They were treated with sulphasalazine (1-4 G/day) for 6-24 wks. There was improvement in all primary outcome measures (morning stiffness, BASFI, patient and doctor global assessment and ESR) in 8 patients.

Pamidronate : 3 patients who were refractory to NSAIDs were treated with inj pamidronate 60 mg IV monthly. At the end of 3 months BASDAI reduced by 47%, BASFI by 43% and BASMI scores by 46%. Side effects of Pamidronate include transient asymptomatic hypocalcaemia, transient lymphopenia, bone pain and infusion site reaction[11] but none of our patient had any toxicity.

Infliximab : Eleven patients with severe active As (as assessed by morning stiffness, nocturnal pain, patient and physicians global assessment, HAQ) were treated with Infliximab (5mg/kg) body weight 0, 2nd and 6th week. There was marked improvement (Table 1):

Table 1: Improvement with infliximab

Parameters	Before Treatment (median value)	During Treatment (median value)	
	0 week	2 weeks	6 weeks
Morning stiffness	120 min	40 min	30 min
Spinal pain (0-3)	2	1	0
Global assessment of the patient (0-100)	69	27	13
Physician global assessment (0-100)	69	27	13
ESR (1st hour)	50 mm	25 mm	14 mm
Tender joint count (0-68)	7	3	1
Swollen joint count (0-68)	4	1	0
BASDAI (0-100)	66.4	17.5	7.2 (p<.001)
BASFI (0-100)	72.4	31.3	9.5 (p<.001)

2 patients did not respond whereas 1 patient had reactivation of uveitis.

The major limitations of Infliximab use are its high costs. Severe types of adverse events are of particular concern : (a) infection– specially tuberculosis, (b) malignancies e.g. lymphoma, (c) anaemia, thrombocytopenia, (d) demyelination, (e) exacerbation of CHF, (f) autoimmune response, (g) hypersensitivity reaction.

So, Infliximab is very much effective in severe active AS and treated patients improve markedly – so as the quality of life is totally changed and there is also less chance of developing deformities. Answers to questions about possible predictors of response to Infliximab, optimal dosing and timing of the start of treatment in the disease courses are also required from future studies.

Physical Therapy :

The goals of physical treatment of AS are to improve mobility and strength and to prevent or reduce spinal curve abnormalities. Physical treatments, including physical therapy and regular exercise, contribute to AS management but cannot replace pharmacotherapy. However, physical treatments and medical treatment are mutually complementary. Physical exercise is impossible until pain and inflammation are medically controlled. However, stiffness and spinal deformities cannot be prevented by drugs alone.

Surgical Intervention :

Surgery may become necessary in some cases of AS. The mechanisms responsible for the ossification of ligaments and joints that causes fusion of the spinal column have not been established. As a result of this process, the fused vertebrae become a long bone housing for the spinal cord, limiting movement and elasticity. The reduction in flexibility renders the spine susceptible to a variety of disorders, including fracture and dislocation, atlanto-axial and atlanto-occipital subluxation, spinal deformity, spinal stenosis, and hip disease. When these complications occur, surgical intervention may be required.

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