Activity Score) (Ann. Rheum. Dis 916,1990). The US Food and Drug Administration has also developed several different labels for drugs in RA including improvement in signs and symptoms, function and quality of life, stabilisation in radiographic progression and complete clinical response and remission.

Methotrexate remains the most most widely studied and popular therapy to treat RA. Leflunomide, the oral pyrimidine inhibitor, was recently approved for RA. One randomised trial of 359 pts compared leflunomide (20 mg/day) to sulfasalazine (2 gr/day) and to placebo (Lancet 353:259,1999). At week 24, 29% of the placebo patients met ACR 20% response criteria compared to 55% in the lef group and 56% in the ssa group. There was less radiographic progression in the lef and ssa group as compared to placebo. In a study of 482 pts leflunomide (20 mg/day) was compared to methotrexate (7.5 to 15.0 mg/wk) and to placebo (Arch. Intern. Med.159:2542,1999). Of those patients who completed 52 weeks of therapy, 41% of patients on lef met an ACR 20% criteria compared to 35% on MTX and 19% on placebo. There was significantly more radiographic progression as measured by Sharp score in those receiving placebo as compared to either MTX or lef (Arthritis Rheum. 43:495, 2000). Leflunomide has received the signs and symptoms claim and the radiographic label.

Infliximab, the chimeric monoclonal antibody, that down regulates TNF activity is the first biologic that reported efficacy in RA. In the pivotal study, 428 patients who had active RA were maintained on chronic MTX therapy and were randomised to receive placebo or one of four dosing regimens of infliximab (Lancet 354, 1932, 2000, NEJM 343:1594, 2000). Patients were dosed with infliximab either every 4 or 8 weeks at doses of either 3.0 or 10.0 mg/kg or placebo. At week 52, there was sustained clinical response with ACR 20% being noted in 52% of the infliximab groups as compared to 17% in the placebo group. At wk 52 a reduction in the rate of radiographic progression was observed with all doses and dosing regimens of infliximab as compared to placebo plus MTX. Infliximab has received the signs and symptoms claim and the radiographic label. Etanercept, the p75 TNF receptor, has been extensively studied in trials in North America. One study of 234 patients with active RA evaluated 25 mg or 10 mg of etanercept injected twice per week versus placebo for 6 months (Ann Intern Med. 130:478, 1999). At month 6, 59% of the 25-mg group and 11% of the placebo achieved an ACR 20% response. In a 24-week double-blind study, 89 patients on chronic MTX patients were randomised to receive either etanercept 25 mg twice a week or placebo (NEJM 340:253,1999). At week 24, 71% of those patients receiving etanercept plus MTX and 27% of those receiving placebo plus MTX met ACR 20% response criteria. In another trial 632 patients with early RA (less than 3 years) were randomised to receive either MTX or etanercept (NEJM 343:1586, 2000). Patients were treated for one year with either etanercept 25 mg twice a week, etanercept 10 mg twice a week or MTX at a dose that was rapidly escalated to a dose of 20 mg/wk. There was a more rapid effect with etanercept as compared to MTX in the first several months of treatment but both drugs lead to significant improvements in ACR response criteria and a reduction in radiographic progression. Etanercept has received the signs and symptoms claim and the radiographic label

Fibromyalgia is a central nervous system disorder – Friday 15 June, 10.00-11.45/ Forum Hall

SP0062 FIBROMYALGIA: EVIDENCE FOR A CENTRAL NERVOUS SYSTEM DISORDER

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This presentation reviews evidence from several studies in our laboratory regarding central factors associated with abnormal pain sensitivity in fibromyalgia (FM). We have found that, compared to healthy controls, clinic patients with FM and community residents who meet criteria for FM but have not consulted a physician (FM non-patients) display significantly lower pain thresholds in response to pressure stimulation and exhibit significantly higher cerebrospinal fluid (CSF) levels of substance P. In addition, during exposure to suprathreshold levels of pressure stimulation, controls and FM patients differ in changes in brain regional cerebral blood flow (rCBF). That is, controls show significant rCBF increases in the contralateral thalamus, somatosensory cortex, and the anterior cingulate cortex, whereas patients with FM show significant and bilateral increases in rCBF in these brain structures. Finally, patients with FM show greater cardiovascular responses to stress than controls. Moreover, stress produces greater increases in thermal pain unpleasantness ratings among FM patients compared to controls. Together, these findings indicate that FM patients show abnormal central processing of nociceptive stimuli that tends to be exacerbated by stress. We plan to determine whether the effects of stress on pain unpleasantness in FM (a) are associated with abnormal rCBF changes in the anterior cingulate cortex; and (2) may be mediated by abnormal cortisol release or cytokine production.

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SP0063 GENETIC FACTORS IN FIBROMYALGIA

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Fibromyalgia (FM) is a syndrome of unknown aetiology characterised by chronic wide spread pain, increased tenderness to palpation and additional symptoms such as disturbed sleep, stiffness, fatigue and psychological distress. Familial aggregation of FM is common. Depressive symptoms and psychological distress is a frequent finding in FM patients and their relatives.¹ These findings suggest that genetic and familial factors may play a role in the etiopathogenesis of this syndrome. In a recent linkage analysis of 40 FM multicase families it was shown that the HLA region might be a candidate for genetic transmission of vulnerability for the disorder.²

The pathophysiological mechanisms underlying fibromyalgia have been linked to disturbances in serotonin (5-HT) metabolism and transmission. Among the different parameters of the serotonin pathway the genes coding for the 5-HT receptors and transporters are interesting candidates to investigate a genetically driven predisposition to FM. Recent studies have analysed silent and functional polymorphic variants of these genes in patients with fibromyalgia.^{3,4,5}

- The human 5-HT transporter (5-HTT) is encoded by a single gene on chromosome 17q12. A functional polymorphism in the transcriptional region has been described ("long allele" L or "short allele" S). In a study of 62 FM patients a higher frequency of the S/S genotype of the 5-HTT was found compared to healthy controls. The S/S subgroup revealed higher means in depression and psychological distress.
- The 5-HT_{2A} receptor gene is located on chromosome 13q14–21. A silent T102C polymorphism of the 5-HT_{2A} receptor gene has recently been detected. In a sample of 168 FM patients a statistically significant different distribution of genotypes was found with a decrease in T/T and an increase in both T/C and C/C genotypes compared to controls. A correlation of genotypes with pain variables revealed higher scores in the tenderpoints score in patients with the T/T genotype. Correlations with psychopathological symptoms were not significant.
- The 5-HT_{2C} receptor gene is located on the X chromosome. In a sample of 65 FM patients the presence of the 5-HT_{2C} (C32S) mutant was significantly correlated with measures of psychological distress. In the same sample the tryptophan hydroxylase (TPH) gene was analysed. The TPH gene is located on the short arm of chromosome 11 and a polymorphism in intron 7 has recently been detected. The TPH is the rate limiting enzyme that determines the concentrations of serotonin *in vivo*. No significant different frequencies of the alleles were found in this group of FM patients compared to control subjects.

The implication of these findings for the etiopathogenesis of fibromyalgia is far from clear and have to be replicated in larger and ethnical different samples. But these results might point to a disturbance on 5-HT-receptor and transporter level at least in a subgroup of FM patients and emphasises the importance of the serotonergic system in the pathophysiology of FM.

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SP0064 DRUG THERAPY IN FIBROMYALGIA. A REVIEW

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Since the cause and pathophysiology of fibromyalgia (FM) remain unknown, treatment is often limited; fewer than 50% of patients have significant and sustained clinical improvement. No pharmacologic agent are indicated specifically for FM treatment, although many have been tried to date. Controlled trials with non-steroidal anti-inflammatory drugs have been shown them to be of little help, despite their use in a majority of patients. Steroidal anti-inflammatory drugs are not efficacious and often deleterious. Among analgesics, preliminary data suggest that tramadol, affecting norepinephrine at the receptor site, may be useful for FM pain. No clinical data are available to suggest efficacy of opioids in FM. Tricyclic antidepressants and selective serotonin reuptake inhibitors may diminish the sleep disturbance, pain and depression associated with FM. they remain the cornerstone of drug therapy in FM. Blockade of the serotonin receptor subtype 5-HT₃ with Tropisetron or Ondansetron has been reported to significantly decrease the number of tender points, despite poor digestive tolerance. The findings of low levels of insulin-like growth factor 1 in FM led to give daily growth hormone (GH) injections to 22 women (vs placebo to 23), enrolled in a controlled study. A 9 months, the tender point score was significantly improved with GH. other agents like 5-hydroxytryptophan, gamma-hydroxybutyrate and S-adenosyl-L-Methionine also shown promising results. FM symptoms may be alleviated in a short term manner with various pharmacologic treatments but a minority of patients still experience remission at a few years follow-up.

SP0065 FIBROMYALGIA: PAIN MANAGEMENT STRATEGIES

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At present, there is no specific treatment for FM, partly because of the lack of understanding of its aetiology and pathogenesis. Self-management based programs have been proposed to help the patients cope with their symptoms and improve their quality of life. These programs mainly use information, physical conditioning, and cognitive-behavioural techniques.

Information in chronic pain patients has been emphasised as an important component as a well-informed patient is an essential member of a successful chronic illness management team. Acknowledging FM patients' pain and suffering is also a key point in these programs.

FM patients have been shown to have functional impairment which include their ability to perform daily activities. They have decreased muscle strength and endurance, and low levels of physical fitness. Exercise programs are various and may include range-of-motion exercises, cycling, walking, swimming, specific muscular reinforcement, etc. Pool exercises have been used in