2008,19(2):247-251

Ενδιαφέροντα Άρθρα Βιβλιογραφίας

Treatment of pulmonary fibrosis for twenty weeks with imatinib mesylate in a patient with mixed connective tissue disease.

Distler JHW, Manger B, Spriewald BM, Schett G, Distler O.
Arthritis Rheum 2008;58:2538-42

Ο αναστολέας της τυροσινικής κινάσης imatinib (Gleevec) σε δόση 400 mg/ημέρα χορηγήθηκε για 20 εβδομάδες σε 64χρονη ασθενή με Μικτή Νόσο του Συνδετικού Ιστού και ταχέως εξελισσόμενη πνευμονική ίνωση παρά την προηγηθείσα αγωγή με ανοσοκατασταλτικά φάρμακα. Η σημαντική βελτίωση που εμφάνισε η ασθενής σηματοδοτεί την πιθανή αποτελεσματικότητα του imatinib σε ασθενείς με νοσήματα που προκαλούν ίνωση**.**

Interstitial lung disease, which is common in patients with mixed connective tissue disease (MCTD), can progress to severe pulmonary fibrosis. The tyrosine kinase inhibitor imatinib mesylate has recently been shown to prevent experimental pulmonary, dermal, and renal fibrosis. Our patient, a 64-year-old woman with MCTD and rapidly progressive pulmonary fibrosis, presented with rapid deterioration despite treatment with immunosuppressants. During 20 weeks of treatment with imatinib mesylate at 400 mg/day, our patient improved significantly according to several outcome measures, including New York Heart Association classification, diffusing capacity for carbon monoxide, 6-minute walking distance, arterial oxygen pressure, and reduction of ground-glass opacities seen on high-resolution computed tomography. No adverse effects of imatinib mesylate were observed. These findings suggest that imatinib mesylate might be effective in patients with fibrotic diseases and warrant the initiation of larger clinical studies on the safety and efficacy of imatinib mesylate in connective tissue diseases.

Prognostic model based on nailfold capillaroscopy for identifying Raynaud's phenomenon patients at high risk for the development of a scleroderma spectrum disorder: PRINCE (Prognostic Index for Nailfold Capillaroscopic Examination).

Ingegnoli F, Boracchi P, Gualtierotti R, Lubatti C, Meani L, Zahalkova L et al.
Arthritis Rheum 2008;58:2174-82

Η παρουσία γιγάντιων τριχοειδικών αγκυλών (loops) και μικροαιμορραγιών καθώς και ο αριθμός των προσβεβλημένων τριχοειδών που αναδεικνύονται σε τριχοειδοσκόπηση της κοίτης των ονύχων, σε ασθενείς με φαινόμενο Raynaud, μπορούν να διακρίνουν εκείνους τους ασθενείς που έχουν υψηλό κίνδυνο εμφάνισης συστηματικής σκληροδερμίας.

Objective: To construct a prognostic index based on nailfold capillaroscopic examinations that is capable of predicting the 5-year transition from isolated Raynaud's phenomenon (RP) to RP secondary to scleroderma spectrum disorders (SSDs).

Methods: The study involved 104 consecutive adult patients with a clinical history of isolated RP, and the index was externally validated in another cohort of 100 patients with the same characteristics. Both groups were followed up for 1-8 years. Six variables were examined because of their potential prognostic relevance (branching, enlarged and giant loops, capillary disorganization, microhemorrhages, and the number of capillaries).

Results: The only factors that played a significant prognostic role were the presence of giant loops (hazard ratio [HR] 2.64, $P = 0.008$) and microhemorrhages (HR 2.33, $P = 0.01$), and the number of capillaries (analyzed as a continuous variable). The adjusted prognostic role of these factors was evaluated by means of multivariate regression analysis, and the results were used to construct an algorithm-based prognostic index. The model was internally and externally validated.

Conclusion: Our prognostic capillaroscopic index identifies RP patients in whom the risk of developing SSDs is high. This model is a weighted combination of different capillaroscopy parameters that allows physicians to stratify RP patients easily, using a relatively simple diagram to deduce the prognosis. Our results suggest that this index could be used in clinical practice, and its further inclusion in prospective studies will undoubtedly help in exploring its potential in predicting treatment response.

Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial.

Galiè N, LJ Rubin LJ, Hoeper MM, Jansa P, Al-Hiti H, Meyer GMB, et al.
Lancet 2008

Η χορήγηση bosentan μπορεί να είναι ευεργετική και για τους ασθενείς με πνευμονική αρτηριακή υπέρταση λειτουργικού σταδίου ΙΙ κατά WHO.

Background: Treatments for pulmonary arterial hypertension have been mainly studied in patients with advanced disease (WHO functional class [FC] III and IV). This study was designed to assess the effect of the dual endothelin receptor antagonist bosentan in patients with WHO FC II pulmonary arterial hypertension.

Methods: Patients with WHO FC II pulmonary arterial hypertension aged 12 years or over with 6-min walk distance of less than 80% of the normal predicted value or less than 500 m associated with a Borg dyspnoea index of 2 or greater were enrolled in this double-blind, placebo-controlled, multicentre trial. 185 patients were randomly assigned to receive bosentan (n=93) or placebo (n=92) for the 6-month double-blind treatment period via a centralised integrated voice recognition system. Primary endpoints were pulmonary vascular resistance at month 6 expressed as percentage of baseline and change from baseline to month 6 in 6-min walk distance. Analyses of the primary endpoints were done with all randomised patients who had a valid baseline assessment and an assessment or an imputed value for month 6.

Results: Analyses were done with 168 patients (80 in the bosentan group, 88 in the placebo group) for pulmonary vascular resistance and with 177 (86 and 91) for 6-min walking distance. At month 6, geometric mean pulmonary vascular resistance was 83,2% (95% CI 73,8 - 93,7) of the baseline value in the bosentan group and 107,5% (97,6 - 118,4) of the baseline value in the placebo group (treatment effect 22,6%, 95% CI 33,5 - 10,0; p<0,0001). Mean 6-min walk distance increased from baseline in the bosentan group (11,2m, 95% CI 4,6 - 27,0) and decreased in the placebo group (7,9 m 24,3- 8,5), with a mean treatment effect of 19,1 m (95% CI 3,6 - 41,8 p=0,0758). 12 (13%) patients in the bosentan group and eight (9%) in the placebo group reported serious adverse events, the most common of which were syncope in the bosentan group and right ventricular failure in the placebo group.

Conclusion: Bosentan treatment could be ben-

eficial for patients with WHO FC II pulmonary arterial hypertension.

An open-label pilot study of infliximab therapy in diffuse cutaneous systemic sclerosis.

Denton CP, Engelhart M, Tvede N, Wolson H, Khan K, Shiwen X et al.
Ann Rheum Dis 2008; Sep. Epud ahead of print.

Η χορήγηση infliximab για 26 εβδομάδες σε ασθενείς με διάχυτη συστηματική σκληροδερμία, αν και δεν έδειξε καμιά σημαντική βελτίωση στη προσβολή του δέρματος, συσχετίστηκε ωστόσο με κλινική σταθεροποίηση και πτώση των επιπέδων του αμινοτελικού προπεπτιδίου του κολλαγόνου τύπου ΙΙΙ στον ορό και της έκκρισης του κολλαγόνου τύπου Ι από τους ινοβλάστες του δέρματος (εργαστηριακοί δείκτες σύνθεσης του κολλαγόνου).

Objective: We have examined the safety and potential efficacy of a chimaeric anti-TNF monoclonal antibody (infliximab) in diffuse cutaneous SSc.

Methods: This was a 26 week open-label pilot study in which 16 cases of dcSSc received 5 infusions of infliximab (5mg/kg). Clinical assessment included skin sclerosis score, scleroderma-HAQ, self-reported functional score and physician global VAS. Collagen turnover, skin biopsy analysis and full safety evaluation was performed.

Results: There was no significant change in skin score at 26 weeks but a trend for lower MRSS at 22 weeks (17, 6-46) compared with peak value (29, 11-44; p=0.10). Serum amino-terminal propeptide of type III collagen (PIIINP) level was significantly lower at week 26 compared with baseline (p=0.03). Secretion of type I collagen by dermal fibroblast was reduced at 26 weeks compared with baseline (p=0.02). There were no deaths during the study and no suspected unexpected serious adverse reactions (SUSARs). There were 21 serious adverse events (SAE) that occurred in 7 subjects, mostly attributable to dcSSc. There were 127 distinct adverse events (AE), occurring in 16 subjects. Of these 19 AE (15%) were probably or definitely related to infliximab treatment. 8 (50%) patients prematurely discontinued infliximab. Anti-infliximab antibodies developed during the study in 5 subjects and were significantly associated with suspected infusion reactions (p=0.025).

Conclusion: In dcSSc infliximab did not show clear benefit at 26 weeks but was associated with clinical stabilisation and fall in two laboratory markers of collagen synthesis. The frequency of suspected infusion reactions may warrant additional immunosuppression in any future studies in SSc.

Antiphospholipid Syndrome. Prevention of murine antiphospholipid syndrome by BAFF blockade.

Kahn P, Ramanujam M, Bethunaickan R, Huang W, Tao H, Madaio MP et al.
Arthritis Rheum 2008;58:2824-34

Η θεραπευτική αναστολή του BAFF σε πειραματικό πρότυπο ποντικών μπορεί να προλάβει ή να θεραπεύσει αντιφωσφολιπιδικό σύνδρομο.

This study was undertaken to determine whether BAFF blockade can be used to prevent or treat antiphospholipid syndrome in a mouse model. Eight- and 12-week-old (NZW x BXSB) F_1 mice were treated with BAFF-R-Ig or TACI-Ig alone or in addition to a short course of CTLA-4Ig. Mice were monitored for thrombocytopenia and proteinuria. Sera were tested for anticardiolipin antibodies (aCL), BAFF levels, and levels of soluble vascular cell adhesion molecule and E-selectin. Mice were killed at 17, 22, or 32 weeks

of age, and kidneys and hearts were subjected to histologic examination. Spleen cells were phenotyped and enzyme-linked immunospot assays for autoantibody-producing B cells were performed. Both BAFF-R-Ig and TACI-Ig prevented disease onset and significantly prolonged survival. Treated mice had significantly smaller spleens than controls, with fewer B cells and fewer activated and memory T cells. BAFF blockade did not prevent the development of aCL, and there was only a modest delay in the development of thrombocytopenia. However, treated mice had significantly less nephritis and myocardial infarcts than did controls. Our findings suggest that aCL are generated in the germinal center, which is relatively independent of BAFF. Effector function of antiplatelet antibodies was only modestly affected by BAFF blockade. In contrast, myocardial infarctions were prevented, suggesting that triggering of thromboses requires both autoantibodies and mediators of inflammation. Similarly, renal damage requires both immune complexes and effector cells. The dissociation between autoantibody production and inflammation that may occur with B cell-depleting therapies underscores the role of B cells as effector cells in the autoimmune response.

Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: Results of a multicenter, randomized, double-blind, active drug-controlled study.

Weinblatt ME, Schiff MH, Ruderman EM, Bingham III CO, Li J, Louie J et al.
Arthritis Rheum 2008;58:1921-30

Η αύξηση της χορηγούμενης δόσης etanercept από 50 mg μία φορά σε 50 mg δύο φορές εβδομαδιαίως σε ασθενείς με ρευματοειδή αρθρίτιδα και ανεπαρκή ανταπόκριση στην αρχική δόση, δεν έδειξε σημαντική βελτίωση στο δείκτη DAS28 μετά από 12 εβδομάδες θεραπείας.

Objective: To evaluate the efficacy and safety of treatment with 50 mg of etanercept twice a week plus weekly methotrexate (MTX; ≥15 mg) in patients with rheumatoid arthritis (RA) who had a suboptimal response to 50 mg of etanercept once a week plus weekly MTX (≥15 mg).

Methods: In this multicenter, randomized, double-blind, active drug-controlled study, suboptimal responders to treatment with MTX plus etanercept 50 mg once weekly were given MTX plus etanercept 50 mg twice weekly (n = 160) or MTX plus etanercept 50 mg once weekly plus a placebo (n = 40) for 12 weeks. In a subsequent 12-week open-label period, patients who responded to etanercept 50 mg twice weekly decreased their dosage to 50 mg once weekly, those who had a partial response to etanercept 50 mg once weekly increased their dosage to 50 mg twice weekly, and those who had no response to etanercept 50 mg twice weekly were discontinued. The primary end point was the proportion of patients with a response on the Disease Activity Score 28-joint assessment (DAS28) at week 12.

Results: A total of 201 patients were randomized; 187 completed 12 weeks, and 102 completed 24 weeks. At week 12 (double-blind period), the DAS28 response in the 50 mg twice weekly and the 50 mg once weekly groups was not significantly different (45.6% versus 35.0%; $P = 0.285$), and similar proportions of patients in the groups taking 100 mg and 50 mg experienced adverse events (34.4% versus 37.5%; $P = 0.711$). Serious adverse events occurred in 7 of 160 of the 50 mg twice weekly group and 0 of 40 of the 50 mg once weekly group ($P = 0.387$), and serious infectious events occurred in 3 of 160 patients in the 50 mg twice weekly group ($P = 0.884$).

Conclusion: Etanercept 50 mg once weekly is an optimal dosage in most patients with RA. Increasing the dosage from 50 mg once weekly to 50 mg twice weekly in suboptimal responders did not significantly improve their DAS28 responses.

Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I/II randomized, blinded, placebo-controlled, dose-ranging study.

Genovese MC, Kaine JL, Lowenstein MB, Del Giudice J, Baldassare A, Schechtman J et al.
Arthritis Rheum 2008;58:2652-61

Η χορήγηση ocrelizumab (ανθρώπειο αντι-CD20 μονοκλωνικό αντίσωμα) σε συνδυασμό με μεθοτρεξάτη σε ασθενείς με ρευματοειδή αρθρίτιδα (κλινική μελέτη φάσεως I/II) ήταν καλά ανεκτή κατά την παρακολούθηση 72 εβδομάδων. Δόσεις ≥200 mg (2 εγχύσεις) έδειξαν καλύτερη κλινική ανταπόκριση, μεγαλύτερη μείωση των επιπέδων της CRP ορού και πολύ χαμηλή αντιγονικότητα.

Objective: Ocrelizumab, a humanized anti-CD20 monoclonal antibody, was studied in a first-in-human trial in rheumatoid arthritis (RA) patients receiving concomitant methotrexate (MTX).

Methods: The ACTION trial was a combined phase I/II study of placebo plus MTX versus ocrelizumab plus MTX in 237 RA patients (intent-to-treat population). During phase I, 45 patients were treated with 1 of 5 escalating doses of study drug (infusions on days 1 and 15, 10-1,000 mg per each infusion). An additional 192 patients were randomized during phase II. Eligible patients had active disease, an inadequate response to treatment with at least MTX, rheumatoid factor positivity, and elevated levels of acute-phase reactants. The total study duration was 72 weeks. B cell pharmacodynamics over time was investigated.

Results: Baseline demographics were similar among the treatment groups. Based on the entire 72-week data set, the incidence of serious adverse events in the ocrelizumab-treated patients was 17.9%, as compared with 14.6% in placebo-treated patients. The incidence of serious infections was 2.0% in all ocrelizumab-treated patients and 4.9% in placebo-treated patients. Infusion-associated adverse events were mostly grade 1 or grade 2 and were more frequent around the time of the first infusion. No serious infusion-associated adverse events were reported in the ocrelizumab group. Evidence of clinical activity was observed at all doses evaluated. Peripheral B cell depletion after infusion was rapid at all doses, with earlier repletion of B cells at doses of 10 mg and 50 mg. Human anti-human antibodies were detected in 19% and 10%, respectively, of those receiving 10 mg and 50 mg of ocrelizumab, compared with 0-5% of those receiving 200, 500, and 1,000 mg.

Conclusion: Ocrelizumab therapy in combination with MTX was well tolerated. Doses of 200 mg (2 infusions) and higher showed better clinical responses, better reduction of C-reactive protein levels, and very low immunogenicity.