Ενδιαφέροντα Άρθρα Βιβλιογραφίας

EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR scleroderma trials and research group (EUSTAR).

Kowal-Bielecka O, Landere R, Avouac R, Chwiesko S, Miniati I, Czirjak L et al.
Ann Rheum Dis published online 19 Jan 2009

Συστάσεις της EULAR για τη θεραπεία της συστηματικής σκληροδερμίας:

I. Αγγειοπάθεια σκληροδέρματος (Φαινόμενο Raynaud και δακτυλικά έλκη)

1. Οι αναστολείς των διαύλων ασβεστίου τύπου διυδροπυριδίνης από το στόμα, όπως η νιφεδιπίνη πρέπει να θεωρείται θεραπεία πρώτης εκλογής για το φαινόμενο Raynaud
2. Η ενδοφλέβια χορήγηση ιλοπρόστης (iloprost, Ilomedin®) ή άλλου διαθέσιμου ενδοφλέβιου προστανοειδούς πρέπει να θεωρείται ως θεραπεία πρώτης εκλογής για το βαρύ φαινόμενο Raynaud ή για την επούλωση ενεργών δακτυλικών ελκών

Το bosentan προλαμβάνει την υποτροπή των δακτυλικών ελκών και πρέπει να χορηγείται για πολλαπλά δακτυλικά έλκη μετά την αποτυχία των αναστολέων των διαύλων ασβεστίου και του προστανοειδούς.

II. Πνευμονική αρτηριακή υπέρταση

Bosentan, ή sitaxentan, ή sildenafil, ή χορήγηση epoprostenol (με σταδιακή διακοπή) έχουν δείξει όφελος και μπορούν να χορηγηθούν για τη θεραπεία της πνευμονικής αρτηριακής υπέρτασης

III. Προσβολή δέρματος

Η μεθοτρεξάτη μπορεί να χορηγηθεί στην πρώιμη διάχυτη δερματική σκληροδερμία

IV. Διάμεση πνευμονική νόσος

Η κυκλοφωσφαμίδη πρέπει να χορηγηθεί για τη θεραπεία της διάμεσης πνευμονικής ίνωσης

V. Νεφρική κρίση σκληροδερμίας

1. Οι αναστολείς του μετατρεπτικού ενζύμου της αγγειοτενσίνης πρέπει να χορηγούνται για τη θεραπεία της νεφρικής κρίσης της σκληροδερμίας
2. Ασθενείς σε αγωγή με κορτικοστεροειδή, λόγω αυξημένου κινδύνου, πρέπει να παρακολουθούνται στενά ως προς την αρτηριακή πίεση και τη νεφρική τους λειτουργία

VI. Προσβολή του γαστρεντερικού σωλήνα

1. Οι αναστολείς της αντλίας πρωτονίων πρέπει να χορηγούνται για την πρόληψη της γαστροισοφαγικής παλινδρόμησης
2. Όταν υπάρχει φούσκωμα ή ψευδοαπόφραξη πρέπει να χρησιμοποιούνται φάρμακα που υποβοηθούν την κινητικότητα του εντέρου
3. Όταν υπάρχει δυσαπορρόφηση από υπερανάπτυξη μικροβίων πρέπει να χορηγούνται αντιβιοτικά.

Tumour-like mass lesion: an under-recognised presentation of primary angiitis of the central nervous system.

Molloy ES, Singhal AB, Calabrese LH
Ann Rheum Dis 2008;67:1732-5

Η πρωτοπαθής αγγειίτιδα του κεντρικού νευρικού συστήματος, και μάλιστα αυτή που σχετίζεται με αμυλοειδές μπορεί να εκδηλωθεί ως όγκος

Objective: To describe the occurrence of mass lesions (ML) in primary angiitis of the central nervous system (PACNS) and assess the utility of diagnostic testing and treatment.

Methods: We examined the case records of the Cleveland Clinic (CC), Massachusetts General Hospital (MGH), and the English language medical literature, for biopsy-proven PACNS cases presenting as a solitary ML. Relevant clinical variables were extracted and analysed with JMP software.

Results: We identified a total of 38 ML: eight of 202 (4.0%) patients with CC/MGH and 30 of 535 (5.6%) patients with PACNS identified from the medical literature. A higher percentage (13 of 45; 29%) was seen in the amyloid-related angiitis subset. Poorer outcomes were reported in the amyloid group, with five deaths. Of the non-amyloid group, better outcomes were seen in the group treated with corticosteroids and cyclophosphamide as compared with the group treated with corticosteroids alone.

Conclusions: Although rare, PACNS should be considered in the differential diagnosis of ML; greater awareness of this manifestation may facilitate more prompt diagnosis and treatment. Biopsy evidence of angiitis is required for diagnosis; specimens should routinely be stained for amyloid. While excision of the lesion may be curative, aggressive immunosuppressive therapy is associated with favourable outcomes and may obviate the need for surgery.

Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study.

van den Bemt BJF, den Broeder AA, Snijders GF, Hekster YA, van Riel PLCM, Benraad B et al.
Ann Rheum Dis 2008;67:1697-701

Σε ασθενείς με ρευματοειδή αρθρίτιδα που λαμβάνουν υψηλότερη δόση (5 mg/kg) ινφλιξιμάμπης (Remicade®), μπορεί να επιτευχθεί ασφαλής και αποτελεσματική ελάττωση της με οδηγό-δείκτη το DAS28

Objectives: In clinical trials only a small subset of patients with rheumatoid arthritis (RA) benefits from higher than standard dose of infliximab (>3 mg/kg/8 weeks). However, dose escalation of infliximab is frequently applied in clinical practice. Individual adjustment of infliximab treatment based on actual disease activity, instead of subjective clinical judgement, could prevent possible unwarranted dose escalation.

Methods: The infliximab dose of all patients with RA treated at our centre was decreased from 5 mg/kg to 3 mg/kg, leaving dosing intervals unaltered. Subsequently patients were followed for at least three infusions. At every visit, 28-joint Disease Activity Score (DAS28), infliximab serum trough levels and anti-infliximab antibody levels were assessed. Inversed European League Against Rheumatism (EULAR) criteria (flare criteria) were used as the endpoint.

Results: A total of 18 patients were included in the study. Mean (SD) DAS28 scores before dose reduction and after first and second low dose were 3.2 (1.2), 3.2 (1.8) and 3.3 (1.2), respectively (values not significant). One patient (6%, 95% CI 0% to 17%) developed a persistent flare that subsided after increasing infliximab doses and one patient stopped infliximab because of a lupus-like reaction. In all other patients (n = 16) lowering infliximab resulted in unaltered disease activity. Infliximab levels showed that most patients had either low- (<1 mg/litre) or high (>5 mg/litre) serum trough levels. Anti-infliximab antibodies were detected in four patients.

Conclusion: Infliximab dosages of 5 mg/kg can be lowered in the majority of patients with RA using DAS28-guided dose titration without increase of disease activity. Lowering the dose of infliximab should be considered in every patient receiving higher doses infliximab.

A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies.

Dastmalchi M, Grundtman C, Alexanderson H, Mavragani CP, Einarsdottir H, Barbasso Helmers S et al.

Ann Rheum Dis 2008;67:1670-7

Η ινφλιξιμάμπη (Remicade®) δεν φαίνεται να είναι αποτελεσματική στην αντιμετώπιση της πολυμυοσίτιδας

Objective: To investigate the effect of the tumour necrosis factor (TNF) blocking agent infliximab in patients with treatment-resistant inflammatory myopathies.

Methods: A total of 13 patients with refractory polymyositis (PM), dermatomyositis (DM), or inclusion body myositis (IBM) were treated with 4 infliximab infusions (5 mg/kg body weight) over 14 weeks. Outcome measures included myositis disease activity score with improvement defined according to The International Myositis Assessment and Clinical Studies Group (IMACS), and MRI. Repeated muscles biopsies were investigated for cellular infiltrates, major histocompatibility complex (MHC) class I and II, TNF, interleukin (IL)1α, IL6, high mobility group box chromosomal protein 1 (HMGB-1), interferon-γ (IFNγ), myxovirus resistance protein A (MxA) and membrane attack complex (MAC) expression. Type I IFN activity was analysed in sera.

Results: Nine patients completed the study. Three patients discontinued due to adverse events and one due to a discovered malignancy. Three of the completers improved by ≥ 20% in three or more variables of the disease activity core set, four were unchanged and two worsened ≥ 30%. No patient improved in muscle strength by manual muscle test. At baseline, two completers had signs of muscle inflammation by MRI, and five at follow-up. T lymphocytes, macrophages, cytokine expression and MAC deposition in muscle biopsies were still evident after treatment. Type I IFN activity was increased after treatment.

Conclusions: Infliximab treatment was not effective in refractory inflammatory myopathies. In view of radiological and clinical worsening, and activation of the type I IFN system in several cases, infliximab is not an alternative treatment in patients with treatment-resistant myositis.

Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: Evidence of a relationship between inflammation and new bone formation.

Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RGW.

Arthritis Rheum 2009;60:93-102

Η φλεγμονή (οίδημα) στη γωνία του σπονδύλου, όπως φαίνεται στη μαγνητική τομογραφία, συσχετίζεται με επακόλουθη ανάπτυξη συνδεσμοφύτων.

Objective: To determine whether a vertebral corner that demonstrates an active corner inflammatory lesion (CIL) on magnetic resonance imaging (MRI) in patients with ankylosing spondylitis (AS) is more likely to evolve into a de novo syndesmophyte visible on plain radiography than is a vertebral corner that demonstrates no active inflammation on MRI.

Methods: MRI scans and plain radiographs were obtained for 29 patients recruited into randomized placebo-controlled trials of anti-tumor necrosis factor α(anti-TNFα) therapy. MRI was conducted at baseline, 12 or 24 weeks (n = 29), and 2 years (n = 22), while radiography was conducted at baseline and 2 years. A persistent CIL was defined as a CIL that was found on all available scans. A resolved CIL was defined as having completely disappeared on either the second or third scan. A validation cohort consisted of 41 AS patients followed up prospectively. Anonymized MRIs were assessed independently by 3 readers who were blinded with regard to radiographic findings.

Results: New syndesmophytes developed significantly more frequently in vertebral corners with inflammation (20%) than in those without inflammation (5.1%) seen on baseline MRI ($P \leq 0.008$

for all reader pairs). They also developed more frequently in vertebral corners where inflammation had resolved than in those where inflammation persisted after anti-TNF treatment. This was confirmed in the analysis of the prospective cohort, in which significantly more vertebral corners with inflammation (14.3%) compared with those without inflammation (2.9%) seen on baseline MRI developed new syndesmophytes ($P \leq 0.003$ for all reader pairs).

Conclusions: Our findings indicate that a syndesmophyte is more likely to develop from a prior inflammatory lesion, supporting a relationship between inflammation and ankylosis.

Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis.

Amin S, Baker K, Niu J, Clancy M, Goggins J, Guermazi A, et al.
Arthritis Rheum 2009;60:189-198

Η μεγαλύτερη μυϊκή ισχύς των τετρακεφάλων μυών πιθανόν προστατεύει την απώλεια αρθρικού χόνδρου στο πλάγιο διαμέρισμα της επιγονατιδομηριαίας άρθρωσης. Ασθενείς με ισχυρούς τετρακεφάλους μυς έχουν λιγότερο πόνο και καλύτερη λειτουργικότητα στα γόνατα

Objective: To determine the effect of quadriceps strength in individuals with knee osteoarthritis (OA) on loss of cartilage at the tibiofemoral and patellofemoral joints (assessed by magnetic resonance imaging [MRI]) and on knee pain and function.

Methods: We studied 265 subjects (154 men and 111 women, mean ± SD age 67 ± 9 years) who met the American College of Rheumatology criteria for symptomatic knee OA and who were participating in a prospective, 30-month natural history study of knee OA. Quadriceps strength was measured at baseline, isokinetically, during concentric knee extension. MRI of the knee at baseline and at 15 and 30 months was used to assess cartilage loss at the tibiofemoral and patellofemoral joints, with medial and lateral compartments assessed separately. At baseline and at followup visits, knee pain was assessed using a visual analog scale, and physical function was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index.

Results: There was no association between quadriceps strength and cartilage loss at the tibiofemoral joint. Results were similar in malaligned knees. However, greater quadriceps strength was protective against cartilage loss at the lateral compartment of the patellofemoral joint (for highest versus lowest tertile of strength, odds ratio 0.4 [95% confidence interval 0.2, 0.9]). Those with greater quadriceps strength had less knee pain and better physical function over followup ($P < 0.001$).

Conclusion: Greater quadriceps strength had no influence on cartilage loss at the tibiofemoral joint, including in malaligned knees. We report for the first time that greater quadriceps strength protected against cartilage loss at the lateral compartment of the patellofemoral joint, a finding that requires confirmation. Subjects with greater quadriceps strength also had less knee pain and better physical function over followup.

Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis.

Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G et al.
Arthritis Rheum 2009;60:219-24

Το Imatinib, που αναστέλλει την τυροσινο-κινάση c-Abl και τον αιμοπεταλιογενή αυξητικό παράγοντα (PDGF) είναι αποτελεσματικό στην αναστολή και βελτίωση της προυπάρχουσας ίνωση σε ποντικούς TSK-1 και σε δερματική ίνωση από bleomycin

Objective: Imatinib is a small-molecule tyrosine kinase inhibitor capable of selective, dual inhibition of the transforming growth factor β and platelet-derived growth factor (PDGF) pathways.

Imatinib has previously been shown to prevent the development of inflammation-driven experimental fibrosis when treatment was initiated before administration of the profibrotic stimulus. The aim of this study was to confirm the efficacy of imatinib in a murine model of systemic sclerosis (SSc) that is less driven by inflammation and to investigate whether imatinib is also effective for the treatment of established fibrosis.

Methods: The tight skin 1 (TSK-1) mouse model of SSc was used to evaluate the antifibrotic effects of imatinib in a genetic model of the later stages of SSc. In addition, the efficacy of imatinib for the treatment of preestablished fibrosis was analyzed in a modified model of bleomycin-induced dermal fibrosis in which the application of bleomycin was prolonged and the onset of treatment was late.

Results: Treatment with imatinib reduced dermal and hypodermal thickening in TSK-1 mice and prevented the differentiation of resting fibroblasts into myofibroblasts. In the model of preestablished dermal fibrosis, imatinib not only stopped further progression of fibrosis but also induced regression of preexisting dermal fibrosis, with a reduction in dermal thickness below pretreatment levels

Conclusion: These results indicate that combined inhibition of the tyrosine kinase c-Abl and PDGF receptor might be effective in the later, less inflammatory stages of SSc and for the treatment of established fibrosis. Thus, imatinib might be an interesting candidate for clinical trials in patients with longstanding disease and preexisting tissue fibrosis.

Spliceosomal peptide P140 for immunotherapy of systemic lupus erythematosus: Results of an early phase II clinical trial.

Muller S, Monneaux F, Schall N, Rashkov RK, Oparanov BA, Wiesel P et al.
Arthritis Rheum 2008;58:3873-83

Χορήγηση σε υποδόρια ένεση πεπτιδίου P140 του ματιασμοσώματος (spliceosoma) σε λίγους ασθενείς με ΣΕΛ φάνηκε ασφαλής

Objective: To assess the safety, tolerability, and efficacy of spliceosomal peptide P140 (IPP-201101; sequence 131-151 of the U1-70K protein phosphorylated at Ser^{140}), which is recognized by lupus CD4+ T cells, in the treatment of patients with systemic lupus erythematosus (SLE).

Methods: An open-label, dose-escalation phase II study was conducted in two centers in Bulgaria. Twenty patients (2 male and 18 female) with moderately active SLE received 3 subcutaneous (SC) administrations of a clinical batch of P140 peptide at 2-week intervals. Clinical evaluation was performed using approved scales. A panel of autoantibodies, including antinuclear antibodies, antibodies to extractable nuclear antigens (U1 RNP, SmD1, Ro/SSA, La/SSB), and antibodies to double-stranded DNA (anti-dsDNA), chromatin, cardiolipin, and peptides of the U1-70K protein, was tested by enzyme-linked immunosorbent assay (ELISA). The plasma levels of C-reactive protein, total Ig, IgG, IgG subclasses, IgM, IgA, and IgE, and of the cytokines interleukin-2 and tumor necrosis factor α were measured by ELISA and nephelometry.

Results: IgG anti-dsDNA antibody levels decreased by at least 20% in 7 of 10 patients who received 3 x 200 μg IPP-201101 (group 1), but only in 1 patient in the group receiving 3 x 1,000 μg IPP-201101 (group 2). Physician's global assessment of disease activity scores and scores on the SLE Disease Activity Index were significantly decreased in group 1. The changes occurred progressively in the population of responders, increased in magnitude during the treatment period, and were sustained. No clinical or biologic adverse effects were observed in the individuals, except for some local irritation at the highest concentration.

Conclusion: IPP-201101 was found to be safe and well tolerated by subjects. Three SC doses of IPP-201101 at 200 μg significantly improved the clinical and biologic status of lupus patients.