

## Ενδιαφέροντα Αρθρα Βιβλιογραφίας

### Κατευθυντήριες οδηγίες των BSR και BHPR για την αγωγή ενηλίκων με αγγειίτιδα που σχετίζεται με ANCA.

Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D et al.

#### **BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis.**

*Rheumatology* 2007;46:1615-16

Η θεραπεία των αγγειιτιδων που συσχετίζονται με ANCA πρέπει να στηρίζεται σε σίγουρη διάγνωση. Περιλαμβάνει θεραπεία εφόδου για 3-6 μήνες με κυκλοφωσφαμίδη και κορτικοστεροειδή και θεραπεία συντήρησης με ήπιότερα φάρμακα για 2-5 έτη.

The ANCA associated vasculitides (AAV) comprise Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyangiitis. Early diagnosis and treatment is important. The aim of this document is to provide guidelines for the management of adults with systemic vasculitis. The diagnosis of vasculitis must be certain. The following criteria must be fulfilled prior treatment:

- A. Symptoms and signs characteristic of systemic vasculitis.
- B. At least one of the following:
  - (a) Histological evidence of vasculitis and/or granuloma formation,
  - (b) Positive serology for ANCA (either cANCA/PR3 or pANCA/MPO),
  - (c) Specific indirect evidence of vasculitis.
- C. No other diagnosis to account for symptoms or signs. It is important to consider other causes of systemic illness, especially malignancy,

infection (particularly bacterial endocarditis) and drugs.

Treatment for vasculitis requires induction of remission followed by maintenance. Current treatment is based on assessing the severity and extent of disease and subdividing the disease into three groups.

#### 1. Induction of remission

##### **(i) Localized/early systemic disease:**

Treatment should be with either cyclophosphamide or methotrexate. Methotrexate may be associated with a higher relapse rate. Localized disease can cause significant local destruction and requires treatment with cyclophosphamide.

##### **(ii) Generalized/organ threatening disease:**

Initial treatment of generalized/organ threatening disease should include cyclophosphamide and steroids. Cyclophosphamide may be given as continuous low dose oral treatment for 3 months or by intravenous pulses initially at 2-week intervals and then 3 weekly for 3-6 months. There is no difference in remission rates and no increased risk of relapse between IV and oral regimens. Continuous low dose oral cyclophosphamide was associated with a higher total cyclophosphamide dosage and a significant increase in infection risk.

##### **(iii). Severe/life threatening disease:**

Patients with AAV presenting with severe renal failure (creatinine >5.6 mg/dL) should be treated with cyclophosphamide (either pulsed IV or continuous low dose oral) and steroids, with adjuvant plasma exchange. Plasma exchange should also

be considered in those with other life threatening manifestations of disease, such as pulmonary haemorrhage.

**Steroids.** Steroids are given as daily oral prednisolone, initially 1 mg/kg up to 60 mg. Intravenous steroids (250–500 mg methylprednisolone) are sometimes given just prior to/with the first two pulses of cyclophosphamide.

## 2. Maintenance therapy

Following achievement of successful remission, cyclophosphamide should be withdrawn and substituted with either azathioprine or methotrexate. Mycophenolate or leflunomide may be used as alternatives for intolerance or lack of efficacy of azathioprine or methotrexate. Patients should continue maintenance therapy for at least 24 months, and in patients with high ANCA for up to 5 years.

### Relapsing disease

Minor relapse is treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression (C). Major relapse is treated with cyclophosphamide with an increase in prednisolone; intravenous methylprednisolone or plasma exchange may also be considered (C).

### Refractory disease

The use of infliximab, intravenous immunoglobulin, antithymocyte globulin, CAMPATH-1H (alemtuzumab, anti-CD52), deoxyspergualin and rituximab in refractory disease is still under investigation (C). It is important to identify potential underlying factors influencing persistent or relapsing disease including infection and malignancy.

### Assessment and monitoring of disease activity

Relapse may occur at anytime. Treatment should not be escalated solely on the basis of an increase in ANCA. Treatment withdrawal

in patients with persistently positive ANCA is associated with relapse.

Preventive measures in immunosuppressed patients

-Mesna should be considered for protection against urothelial toxicity .

- Trimethoprim/sulfamethoxazole (or aerolized pentamidine) should be used as prophylaxis against pneumocystis jiroveci .
- Antifungal prophylaxis treatment should be used .
- Staphylococcal aureus treatment with long-term nasal mupirocin should be considered .
- Female patients should be screened for cervical intraepithelial neoplasia.
- Patients should be counselled about the possibility of infertility following cyclophosphamide treatment .
- Prophylaxis against osteoporosis should be used on all patients receiving high dose corticosteroids.
- Patients receiving immunosuppression should be screened for TB.
- Patients receiving immunosuppression should be vaccinated against pneumococcal infection and influenza.
- Cardiovascular and thromboembolic risk should be assessed

**Οι βιοδείκτες προβλέπουν την ακτινολογική πρόοδο σε αρχικά στάδια ρευματοειδούς αρθρίτιδας και έχουν καλή απόδοση συγκρινόμενοι με τους παραδοσιακούς δείκτες.**

Young-Min S, Cawston T, Marshall N, Christgau S, Saxne T, Robins T et al.

**Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers.**

*Arthritis Rheum 2007;56:3236-47*

Βιοδείκτες, όπως η μεταλλοπρωτεϊνάση-3 (MMP-3) και το καρβοξυτελικό πεπτίδιο του

κολλαγόνου τύπου II (CTX-II) είναι προγνωστικοί δείκτες ακτινολογικής βλάβης των αρθρώσεων στη ρευματοειδή αρθρίτιδα

**OBJECTIVE:** To evaluate the performance of biochemical and traditional markers in predicting radiographic progression in rheumatoid arthritis (RA).

**METHODS:** One hundred thirty-two patients with early RA were treated with nonbiologic therapies for 2 years and studied longitudinally. Genomic DNA was analyzed for presence of the shared epitope. Levels of matrix metalloproteinases (matrix metalloproteinase 1 [MMP-1], MMP-13, and MMP-3), tissue inhibitor of metalloproteinases 1 (TIMP-1), and cartilage oligomeric matrix protein (COMP) were assessed in serially obtained serum samples. The presence of pyridinoline (Pyr), deoxypyridinoline, glycosylated Pyr (Glc-Gal-Pyr), and C-telopeptide of type II collagen (CTX-II) was assessed in urine samples. Radiographs obtained at entry and at 2 years were evaluated using the modified Larsen score.

**RESULTS:** Baseline and 2-year radiographs were available from 118 patients. Larsen scores worsened during the 2 years in 50 patients, while 68 patients had no radiographic progression. Levels of a variety of biochemical markers, i.e., MMP-3, CTX-II, COMP, TIMP-1, Pyr, and Glc-Gal-Pyr, correlated significantly with radiographic progression at entry and longitudinally as assessed by area under the curve (AUC). By multivariate analysis, a model including MMP-3 and CTX-II was identified as providing the best prediction of radiographic progression at entry (predictive accuracy by receiver operating characteristic [ROC] AUC = 0.76 [95% confidence interval 0.66-0.85]), while a combination of MMP-3, CTX-II, and swollen joint count formed the best longitudinal AUC model (predictive accuracy by ROC AUC = 0.81 [95% confidence interval 0.73-0.89]). Patient-reported measures (Health Assessment Questionnaire, pain scores) were of limited use. In a subset of 50 patients who were

treated with methotrexate (MTX) during the followup period, median serum MMP-3 levels decreased after the initiation of MTX therapy ( $P = 0.0003$ ).

**CONCLUSION:** These results indicate that biochemical markers are useful predictors of radiographic progression in RA and that serum MMP-3 levels decrease significantly with MTX therapy. Multivariate models that include MMP-3 and CTX-II perform better than existing traditional markers in predicting radiographic outcome in RA.

---

**Ελάττωση της επίπτωσης του εμφράγματος του μυοκαρδίου σε ασθενείς με ρευματοειδή αρθρίτιδα που ανταποκρίνονται στη θεραπεία με αντι-TNFα: αποτελέσματα από την British Society for Rheumatology Biologics Register.**

W. G. Dixon, K. D. Watson, M. Lunt, K. L. Hyrich, A. J. Silman, D. P. M. Symmons.

**Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor α therapy: Results from the British Society for Rheumatology Biologics Register.**

*Arthritis Rheum 2007;56:2905-12*

Οι ασθενείς με ρευματοειδή αρθρίτιδα που ανταποκρίνονται στη θεραπεία με αντι-TNFα παράγοντες έχουν σημαντική μείωση του κινδύνου εμφράγματος.

**OBJECTIVE:** Rheumatoid arthritis (RA) is associated with an increased risk of coronary artery disease, possibly acting via shared mechanisms of inflammation. This study was undertaken to test the hypothesis that the powerful anti-inflammatory effect of anti-tumor necrosis  $\alpha$  (anti-TNF $\alpha$ ) therapy might lead to a reduction in the incidence of myocardial infarction (MI) in patients with RA.

**METHODS:** Using data from the British Society for Rheumatology Biologics Register, a national prospective observational study, we compared MI

rates in 8,670 patients with RA treated with anti-TNF  $\alpha$  and 2,170 patients with active RA treated with traditional disease-modifying antirheumatic drugs (DMARDs).

RESULTS: Through July 2006, 63 MIs occurred in the anti-TNF $\alpha$  cohort during 13,233 person-years of followup and 17 MIs occurred in the DMARD cohort during 2,893 person-years of followup, equivalent to a rate of 4.8 events per 1,000 person-years and 5.9 events per 1,000 person-years, respectively. After adjustment for baseline risk factors, there was no reduction in the rate of MI in the anti-TNF $\alpha$  cohort compared with the DMARD cohort (incidence rate ratio 1.44 [95% confidence interval 0.56-3.67]). In an analysis of anti-TNF $\alpha$ -treated patients who responded to the treatment within 6 months versus those who did not, MI rates were found to be 3.5 events per 1,000 person-years in responders and 9.4 events per 1,000 person-years in nonresponders. The adjusted incidence rate ratio (95% confidence interval) for responders compared with nonresponders was 0.36 (0.19-0.69).

CONCLUSION: These results indicate that RA patients treated with anti-TNF $\alpha$  do not have a lower incidence of MI compared with RA patients treated with traditional DMARDs. However, the risk of MI is markedly reduced in those who respond to anti-TNF $\alpha$  therapy by 6 months compared with non-responders. This finding supports the notion that inflammation plays a pivotal role in MI.

---

**Μια τυχαίοποιημένη, ελεγχόμενη με placebo δοκιμή του infliximab με μεθοτρεξάτη για τη θεραπεία της πολυαρθρικής μορφής της νεανικής ρευματοειδούς αρθρίτιδας.**

Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G et al.

**A randomised placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis.**

*Arthritis Rheum 2007;56:3096-3106*

Σε ασθενείς με επιμένουσα πολυαρθρική μορφή

της νεανικής ρευματοειδούς αρθρίτιδας παρά τη θεραπεία με μεθοτρεξάτη, η δόση 6 mg/Kg remicade είχε καλύτερο προφίλ ωφέλειας/κινδύνου σε σχέση με τη δόση 3 mg/Kg.

OBJECTIVE: To evaluate the safety and efficacy of infliximab in the treatment of juvenile rheumatoid arthritis (JRA).

METHODS: This was an international, multicenter, randomized, placebo-controlled, double-blind study. One hundred twenty-two children with persistent polyarticular JRA despite prior methotrexate (MTX) therapy were randomized to receive infliximab or placebo for 14 weeks, after which all children received infliximab through week 44. Patients received MTX plus infliximab 3 mg/kg through week 44, or MTX plus placebo for 14 weeks followed by MTX plus infliximab 6 mg/kg through week 44.

RESULTS: Although a higher proportion of patients in the 3 mg/kg infliximab group than in the placebo group had achieved responses according to the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) criteria for improvement at week 14 (63.8% and 49.2%, respectively), the between-group difference in this primary efficacy end point was not statistically significant ( $P=0.12$ ). By week 16, after the crossover from placebo to infliximab 6 mg/kg when all patients were receiving infliximab, an ACR Pedi 30 response was achieved in 73.2% of all patients. By week 52, ACR Pedi 50 and ACR Pedi 70 responses had been reached in 69.6% and 51.8%, respectively, of patients. Infliximab was generally well tolerated, but the safety profile of infliximab 3 mg/kg appeared less favorable than that of infliximab 6 mg/kg, with more frequent occurrences of serious adverse events, infusion reactions, antibodies to infliximab, and newly induced antinuclear antibodies and antibodies to double-stranded DNA observed with the 3 mg/kg dose.

CONCLUSION: While infliximab at 3 mg/kg and 6 mg/kg showed durable efficacy at 1 year, achievement of the primary efficacy end point

at 3 months did not differ significantly between infliximab-treated and placebo-treated patients. Safety data indicated that the 6-mg/kg dose may provide a more favorable risk/benefit profile. These results warrant further investigation in children with JRA.

---

**Η πορεία της ψωρίασης μετά από μείωση των Β-κυττάρων με rituximab.**

Dass S, Vital EM, Emery P.

**Development of psoriasis after B cell depletion with rituximab.**

*Arthritis Rheum 2007;56:2715-8*

Σε 3 ασθενείς που έλαβαν για διάφορους λόγους θεραπεία με rituximab αναπτύχθηκε ψωρίαση

The B cell-depleting monoclonal antibody rituximab is a novel therapy for the rheumatic diseases, with an increasing body of evidence

regarding its safety and efficacy in an expanding range of indications. However, there is uncertainty over its potential use in, and impact on, autoantibody-negative diseases. We describe 3 patients, with no known risk factor for psoriasis, who developed psoriasis (and 1 who also developed features of psoriatic arthritis) after receiving rituximab for a variety of indications, namely, seropositive and seronegative rheumatoid arthritis and systemic lupus erythematosus. In all cases, the underlying disease responded well to rituximab. The interpretation of this possible side effect of rituximab remains unclear, but a B cell-depleted environment may induce abnormal T cell responses, possibly provoked either by subclinical infection or by the removal of mechanisms whereby B cells regulate T cells. These cases suggest that the pathogenesis of psoriasis may not require normal numbers of B cells and that proposed treatment of psoriasis and psoriatic arthritis with rituximab may result in unpredictable responses.