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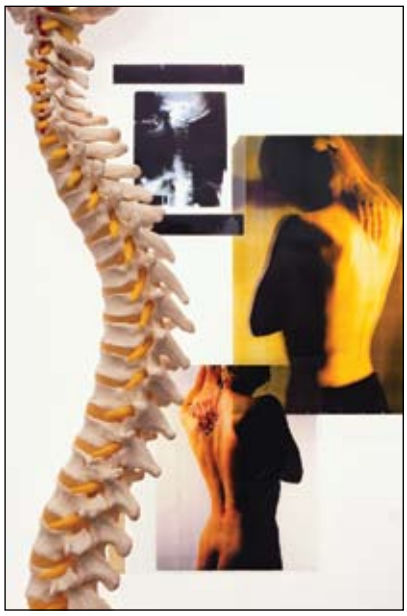
Updates in Rheumatoid Arthritis



Diagnosis and treatment of early rheumatoid arthritis (RA) is challenging because there is no single test that can be used. According to Professor Deborah Symmons, University of Manchester School of Medicine, Manchester, UK, to implement an early intervention strategy, it's essential to identify those patients whose arthritis will evolve into RA and to be able to document treatment response so that therapy can be escalated if necessary. She offered the following guidelines:

- Assessment: Does the patient have inflamed joints? How many? How severe (ESR/CRP)? Is there already evidence of X-ray damage? Does the patient have a positive RF? If not, does the patient have anti-CCP abs?
- Treatment: Aim for remission. Get there as fast as possible. Select therapy based on disease severity. Finally, re-assess the patient regularly in a standardized way

Dr. Hilary Capell, Centre for Rheumatic Disease, Glasgow, UK, discussed the results of two trials using different approaches to therapy. The TIght COntrol for Rheumatoid Arthritis (TICORA) (*Nature Clin Pract Rheumatol.* 2005;1:2-3) trial compared intensive individualized outpatient management of RA with routine outpatient care. Patients in the routine-care group saw a rheumatologist once every 3 months and had their drug therapy adjusted at the discretion of the physician after a clinical examination. The patients in the intensive-treatment group visited a rheumatologist once a month and had formal DAS assessment at each visit. Treatment was stepped up if the DAS44 score was above 2.4 at any visit; if the DAS44 score was below 2.4 for two consecutive (three monthly) visits, treatment was reduced to the 'previous step'. Results indicated that patients treated intensively with conventional DMARDs were more likely to have a good EULAR response or be in remission than patients treated with standard outpatient care (65% versus 16%, $p<0.0001$).

The MASCOT [http://www.arc.org.uk/about_us/pdfs/annrep05.pdf] trial was designed to determine whether patients with a suboptimal response to sulfasalazine (SSZ) would benefit from changing to methotrexate (MTX) or

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from taking both drugs in combination. Of the 166 patients randomized to the 3 groups in the trial (after 6 months treatment with SSZ), 118 completed the study (SSZ 41/55; MTX 38/54; combination 39/56). Patients in the SSZ + MTX group had a better clinical response than those on either drug alone, with no difference in side-effects. "The findings will have a direct benefit to people with rheumatoid arthritis," said Professor Capell. "We now have firm evidence of the benefit of combination therapy with these two drugs."

Results of several trials focusing on the treatment alternatives for RA were presented. The PROMPT (*Arthritis Rheum*. 2004; 50:3432-3443) study was a prospective, double-blind, multicenter RCT conducted to determine whether patients with undifferentiated arthritis who fulfilled the old critieria for probable RA would benefit from treatment with MTX. Patients (n=110) fulfilling the ACR 1958 criteria for probable RA received MTX 15mg/wk or placebo. Disease activity scores (DAS) were checked every 3 months and dosage was increased by 5mg (or 2 placebo tablets) if the DAS was >2.4. After 12 months, study medication was phased out. Patients diagnosed with RA during follow-up continued treatment with MTX. In this study, fewer patients in the MTX group developed RA (20 vs 29) and more achieved remission (18 vs 11) when compared with patients receiving placebo (p=0.02). According to Professor Henrike von Dongen, University of Leiden Medical Center, Leiden, the Netherlands, "One of the most interesting findings from the study was that the patients who benefited the most were the ones showing a positive anti-CCP test, which would, in general, indicate that a patient has a very high likelihood of developing full-blown RA. However, this study indicates that the progression to a full-blown disease amongst these patients could be influenced."

Early and aggressive treatment of RA has been encouraged as a way to minimize inflammation and prevent irreversible joint damage (*Arth Rheum* 2005;52:3381-90). The Toronto Early Arthritis CoHort (TEACH) study was conducted to determine the adequacy of aggressive DMARD therapy in patients with early RA. Sixty percent (56/94) of the patients were treated with 20-25mg of MTX (30% sc) + hydrochloroquine (HCQ) ± SSZ. The remaining 40% received single DMARD therapy. Steroids (prednisone or triamcinolone) were used as bridge therapy until the DMARD took effect. Dosage was adjusted every 3 months to target remission (DAS-CRP <2.6, SDAI ≤3.3, and CDAI ≤2.8). At 12 months, 50% of the 45 evaluable patients achieved remission by DAS criteria (17% SDAI; 20% CDAI) indicating that additional studies in "real world" cohorts should be conducted.

Results of a study comparing the efficacy of MTX alone, or in combination with infliximab (IFX), or IV pulse methylprednisolone (MP) indicate that MTX + IFX and MTX + IV MP are clinically superior to MTX alone and that IFX was superior to MTX in reducing the signs of synovitis and bone edema. Forty-four (44) patients with disease duration <1 year were randomized to receive MTX (up to 20mg/wk) alone or in combination with IFX (3mg/kg) or IV MP (1g). Clinical outcome measures included the DAS28/CRP, ACR 20, 50 and 70, response rates, DAS (<2.6), and time to good response (EULAR criteria). Gadolinium-enhanced MRI of MCPs, wrists, and MTPs were performed at baseline and weeks 18 and 52. Images were semi-quantitatively scored for synovitis, erosions, and bone edema. At week 22, ACR 20, 50 and 70 scores were significantly higher in both the IFX and MP groups versus MTX. MRI synovitis (MTX p=0.026, IFX and MP p<0.0001) and bone edema scores (MTX p=0.029, IFX p=0.049, MP p=0.0002) significantly improved over time in all groups. Erosion scores worsened in all groups but less so in the IFX group compared with the MP group.

The FINnish Rheumatoid Arthritis Combination (FIN-RACo)(*Arthritis Rheum.* 2005; 52:36-41) trial is the first to study the effect of single versus combination DMARD treatment on sustained (24 month) remission in patients with early RA. Remission was defined using the American Rheumatism Association (ARA) scale (excluding fatigue) or DAS28 <2.6. Sustained remission was defined as continued remission at 6, 12, and 24 months. Ninety seven (97) patients were randomized to receive combination therapy; 98 to single therapy. At the end of 2 years, significantly more patients in the combination group were in remission versus the single therapy group (ARA scale 42% vs 20%; DAS28 68% vs 27% combination and single, respectively). Remission was also more often sustained (14%; and 51%, single and combination respectively).

At what point should therapy be switched to the new biologics? According to Dr. Ronald Vollenhoven, Department of Rheumatology, Karolinska Hospital, Stockholm, Sweden, RA patients should be treated aggressively first with DMARDs and glucocorticoids. They should be assessed at least every 3 months and switched to anti-TNF therapy if remission is not achieved.

Sooner or later every clinician has a patient who is refractory to treatment. Dr. Edward Keystone, University of Toronto, Canada, suggested several strategies for management of patients on TNF inhibitor therapy with persistent moderate to severe disease activity: optimizing conventional DMARDs in combination with the TNF inhibitor (TI), switching TIs, or switching to a non-TNF biologic agent. MTX treatment can be optimized by increasing the dose to 25mg, changing from oral to subcutaneous administration, or splitting the dose. An alternative would be to change the concomitant DMARD. The second approach is to consider increasing the dose or reducing the dosing interval of the TIs (data to support this is sparse). Finally, consideration should be given to changing to a non-TNF directed therapy, one which modulates the T-cell response through blockade of co-stimulation or B-cell directed therapy which inhibits both B and T-cell activity.

According to Dr. Josef Smolen, Vienna Medical University, Vienna, Austria, current therapies for RA have limited efficacy. He explained that 30% to 60% of patients do not achieve ACR50 response and that 55% to 75% do not achieve ACR70. Additionally, remission when defined by strict criteria (e.g., SDAI/CDAI) is not sufficiently frequent in trial and clinical practice (even with the new biologics).

He believes, however, that over the past decade the field of RA has experienced incredibly fast advances and continues to move in new directions. Two recently licensed therapies abatacept, a so-called co-stimulation blocker that appears to interfere with activation of T-cells, and rituximab (which depletes B lymphocytes), show promise for patients who are insufficiently responsive to TNF-blockers and existing therapy. Leflunomide has been shown to be clinically effective and to retard joint damage. Three studies published within the last 2 years confirmed the efficacy of MTX + biologic therapy (*Lancet*. 2004;363:675-81; *Arthritis Rheum*. 2004;50:3432-43; *Arthritis Rheum*. 2006;54:26-37).

Looking to the future, Dr. Smolen believes that we need more efficacious and safe combinations including anti-osteoclasts (OCs) + anti-inflammatories and triple therapy (anti-OC + anti-inflammatory 1 + anti-inflammatory 2). He places IL-1, IL-6, and TNF cytokines in the category of "recent therapies" along with the ligand RANKL inhibitors and the biphosphonates. A bit further down the line is the potential for therapies that can target inflammatory mediators through gene products or modification of signal transduction.