Evidence-based Rheumatology

edited by M. Matucci-Cerinic

Much precious time is wasted in frantic Medline searches to find clues in the current literature to a correct diagnosis, prognosis or treatment. With our new section on "Evidence-Based Rheumatology" we intend to provide a regular column in which the most significant studies in the recent literature are presented. Aimed at practitioners and researchers interested in following the latest developments in their field but with too little time to do so, we will select papers published in the last two years that highlight specific problems or provide important new clues in a given area, summarise their contents (aims, methods, results, and discussion), and invite a leading expert to comment on their significance.

Our selection criteria will be rigorous - regarding treatment and prevention only innovative papers with significant results will be presented. Diagnostic studies must include groups of patients both with and without the target disease, the protocol must include the gathering of laboratory and instrumental as well as clinical data, and tests must be analysed and interpreted blindly. In prognostic studies, the patients at the moment of their selection must not present the clinical symptom that is being studied, while more than 70% should have developed the symptom before the end of the study.

The combination of methotrexate, sulfasalazine and hydroxychloroquine is highly effective in rheumatoid arthritis

Authors: J.R. O'Dell *et al.*
Title: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications.
Source: *N Engl J Med* 1996; 334: 1287-91.

Aim: Rheumatoid arthritis (RA) may show a sub-optimal response to treatment with one or two modifying anti-rheumatic drugs (DMARDs). For this reason a two-year double-blind randomized controlled study was carried out to verify the efficacy and safety of combination therapy with three DMARDs (methotrexate + sulfasalazine + hydroxychloroquine) in comparison to treatment with two DMARDs (sulfasalazine + hydroxychloroquine) or methotrexate (MTX) alone.
Methods: 102 patients with active RA and a poor response to at least one of the currently used DMARDs were divided randomly into three groups: (i) 36 received MTX alone at a dosage of 7.5 - 17.5 mg/week (in increasing dosages in the attempt to reach RA remission); (ii) 35 received sulfasalazine (SSz) 550 mg twice daily plus hydroxychloroquine (HC) 200 mg twice daily; and (iii) 31 received MTX + SSZ + HC. The patients were assessed at the third, sixth and ninth months. In those who did not show a ≥ 50% improvement by the ninth month, the treatment was considered to be ineffective, while those who improved by 50% or more were examined every 3 months for the remainder of the two-year study period.
The primary end point was an improvement in the patient's condition by at least 50%, based on the fullfillment of at least 3/4 of the modified Paulus composite criteria for RA improvement, i.e.: morning stiffness (MS) < 30 min. duration, or decreased by 50%; both joint tenderness and joint swelling decreased by 50%, erythrocyte sedimentation rate (ESR) < 30 mm/hr in women and < 20 mm/hr in men. Patients who did not reach this degree of improvement at any of the 3-month evaluations after receiving maximal therapy were considered treatment failures.
Additional parameters were: MS duration, Ritchie index, the patient's global status and level of overall pain, and the physician's global assessement (both scored on a visual analogue scale). All patients underwent an ophthalmologic evaluation every 6 months (for ocular hydroxychloroquine toxicity); an ESR determination every 3 months; and determinations of serum aspartate aminotransferase, albumin and creatinine concentrations monthly.
Results: 13 of the initial 102 patients discontinued the study because of drug toxicity (7 in the MTX group, 3 in SSZ+HC group and 3 in the three drug-group). 37 discontinued for lack of efficacy, and 2 were dropped because they failed to provide their laboratory results.
The remaining 50 patients completed the two-year study, showing at least a 50% improvement at 9 months and maintaining this for the study duration without major drug toxicity. Among these, 24/31 (77%) were taking the 3-drug combination, 14/35 (40%) were taking SSz + HC, and 12/36 (33%) were taking MTX alone ($p = 0.003$ and $p < 0.001$ for the respective comparisons between the three-drug group and the other two groups). Regarding the other measures of efficacy (MS duration, Ritchie index, patient's global status and level of overall pain, physician's global assessement) trends toward clinical improvement in the three-drug group compared with the other two groups were seen which were particularly impressive at two years.
Conclusions: This study demonstrates the efficacy and benefit of combination therapy with MTX + HC + SSZ compared to MTX alone (still considered to be the optimal DMARD for RA) for long-term treatment (2 years). Use of this combination may be efficacious in the earliest phase of the disease to slow RA progression and reduce the risk of joint damage.

Comment

This work is a seminal study on combination therapy for the treatment of RA. It was carefully done and convinced many in the rheumatological community that such combination therapy is both effective and well-tolerated. Of course, there is no such thing as a "perfect study", so there are a few aspects of this study that leave some questions open: (1) the particular dosages of medications chosen (especially 1 qm qd sulfasalazine) leave unanswered the question of what the "best" combination might be; (2) the endpoint of efficacy used is not the standard one [the ACR Response Criteria would have been preferred (1)] which makes it difficult to compare this study to

others; (3) the exceptional safety reported for this triple combination (11% drop-outs on the triple combination vs. 22% on MTX) needs to be corroborated; and (4) the high drop-out rate resulted in a study whose size was small enough to make one wish for a corroborating study.
Despite these shortcomings, this study certainly has solidified a change in treatment philosophy which has been advocated by others [notably Wilske and Healey (2)] in the past.

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2. WILSKE KR, HEALY LA: Challenging the therapeutic pyramid: A new look at treatment strategies for rheumatoid arthritis. *J Rheumatol* 1990; 25 (Suppl. November): 4-7.

Topical non-steroidal anti-inflammatory drugs are effective in acute and chronic pain conditions

Authors: R.A. Moore *et al.*
Title: Quantitative review of topically applied non-steroidal anti-inflammatory drugs.
Source: *British Medical Journal* 1998; 316: 333-8.

Aim: Topical NSAIDs represent an alternative to oral non-steroidal anti-inflammatory drugs (NSAIDs), which may often cause severe adverse gastrointestinal effects. In a systematic review Moore *et al.* examined whether topical NSAIDs are safe and effective, and if various topical preparations show different degrees of efficacy in the treatment of acute and chronic pain conditions.
Methods: A search of the Medline (1966 to September 1996), Embase (1981 to September 1996), and Oxford Pain Relief (1950 to 1994) databases was carried out to identify randomised controlled trials comparing topical NSAIDs with either placebo, another NSAID or an oral NSAID. In addition, pharmaceutical companies in the UK were invited to report the results from their files of randomised controlled trials of NSAIDs. Only trials considering pain as a clinical outcome in acute (soft tissue trauma, strains, and sprains) or chronic conditions (osteoarthritis and tendinitis) were chosen. Treatment success was considered to be a ≥ 50% reduction in pain, and local and systemic adverse effects had to have been analysed at one week from the study start for acute conditions and at 2 weeks for chronic conditions. The quality of each of the studies under consideration was assessed on a scale from 1 to 5. A scattergram was used to analyse the distribution of success rates with NSAID against the success rate with placebo. A random effect model was used to calculate the relative risk or benefit (95% confidence interval) of treatment, based on pain data from placebo-controlled studies, and the data on efficacy was used to calculate "the number needed to treat" (i.e., to obtain a successful outcome compared with placebo) (95% CI).
Results: 86 reports (10,160 patients) fulfilling the inclusion criteria were found. These were divided into two groups (acute and chronic pain) which were then subdivided into groups based on the study design (placebo or active controlled).
For acute pain conditions, placebo had a relative benefit of 1.7 (1.5 - 1.9), and the number needed to treat was 3.9 (3.4 - 4.4). Pooling the data for each drug that had been studied in three or more trials showed ketoprofen, felbinac, ibuprofen and piroxicam to be significantly superior to placebo (the number needed to treat being 2.6, 3.0, 3.5, and 4.2, respectively), while benzydamine and indomethacin did not differ significantly from placebo.
For chronic pain, placebo had a relative benefit of 2.0 (1.5 - 2.7); the number needed to treat was 3.1 (2.7 - 3.8). It is interesting to note that trials with less than 40 pts. overestimated the effectiveness of topical NSAIDs (by 33%) in patients with acute conditions but not in those with chronic conditions.
Five studies (3 of acute and 2 of chronic pain conditions) comparing topical with oral NSAID preparations did not show a significantly greater benefit with oral NSAID. No relationship between the quality of the trial and the treatment effect was found. Local and systemic adverse effects and dropout rates were very low and similar to placebo in both groups.
Conclusions: Topical NSAIDs are effective and safe for acute and chronic conditions. For the treatment of rheumatic pain, topical NSAIDS can be considered a satisfactory alternative to oral and intramuscular NSAIDs. The partial substitution of oral with topical NSAIDs, particularly in cases of chronic pain, could significantly reduce gastrointestinal side effects without sacrificing the anti-inflammatory benefits of NSAIDs.

Comment

Primum non nocere *(first do no harm) is a wise motto in medicine. Although there is no doubt regarding the necessity and efficacy of NSAIDs in chronic rheumatic diseases, the price paid for this treatment can be quite high. Therefore, alternatives are very welcome. One interesting possibility is the use of topically applied non-steroidal anti-inflammatory drugs.*
Moore et al. evaluated, according to by now widely used meta-analysis methods, the available evidence regarding the use of topical NSAIDs. Their data are quite convincing; they found that topical NSAIDs are effective in reducing pain in acute and chronic rheumatic conditions. Interestingly, we have no idea about the exact mechanisms involved in this pain relief. How much is due to the pharmacological effects of the topical NSAID and how much to psychological effects ? Nevertheless, the effects are positive and safe; it is therefore a pity that these topical NSAIDs are not available in all European countries, and that in those cases where they are available, they are not always covered by the national health care system. It would be interesting to see the results of cost-effectiveness studies on the (adjuvant) use of topical NSAIDs in acute and chronic rheumatic pain.

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