

PostScript

MATTERS ARISING

HLA-DR-DQ haplotypes and genotypes in Finnish patients with rheumatoid arthritis

We read with great interest the paper by Laivoranta-Nyman *et al.*¹ They studied Finnish patients with rheumatoid arthritis (RA) and controls, and suggested that there exist susceptibility, neutral and protective HLA-DR-DQ haplotypes that do not match the predictions of current hypotheses for the mechanism of association of the HLA class II region and RA.

The analysis performed, however, does not take into account the effect of marked over-representation of some HLA-DRB1 alleles among the cases on the relative frequencies of other alleles in the cases and controls. We believe that this is the reason for the unexpected findings. If a relative predispositional effects model is used, which does take this bias into account, it can be seen that the results are quite different (table 1).

We have called alleles "significant" if they achieved a Bonferroni corrected p value of <0.05, correcting for 21 alleles (equivalent to an uncorrected p value of <0.0024). This analysis shows that five haplotypes are over-represented:

(DRB1*0401-DQA1*03-DQB1*0301; DRB1*0408-DQA1*03-DQB1*0301; DRB1*0401-DQA1*03-DQB1*0302; DRB1*0404-DQA1*03-DQB1*0302; DRB1*(01/10)-DQA1*01-DQB1*0501), and that all other haplotypes are not significantly different from neutral ($p_{\text{corr}} > 0.2$). All these haplotypes have previously been shown to be associated with RA, and carry the HLA-DRB1 shared epitope.

These findings do not support either the Zanelli/rheumatoid arthritis protection model,² or the model proposed by de Vries *et al.*,³ as no protective haplotypes were observed. The lack of support for these models may represent type II error, and the question of the protective effect of DRB1*0103 has not been dealt with because the DRB1*1 subtype was not further subdivided. None the less, in general, the results are most consistent with the shared epitope hypothesis.⁴

Our analysis agrees with the finding that different DRB1*0401-DQ haplotypes have different strengths of disease association.

This is consistent with previous studies, which demonstrate differential association of major histocompatibility complex (MHC) class III-DRB1*0401 haplotypes with RA (reviewed by Newton *et al.*⁵). What the true disease associated gene is on these haplotypes is as yet unknown, but the findings of Laivoranta-Nyman *et al.*¹ strongly support the existence of further MHC genes influencing RA.

S Harney, B P Wordsworth, M A Brown
 University of Oxford Institute of Musculoskeletal Sciences, Botnar Research Centre, Oxford, UK

Correspondence to: Professor M A Brown, mbrown@well.ox.ac.uk

References

- 1 Laivoranta-Nyman S, Mottonen T, Hermann R, Tuokko J, Luukkainen R, Hakala M, *et al.* HLA-DR-DQ haplotypes and genotypes in Finnish patients with rheumatoid arthritis. *Ann Rheum Dis* 2004;63:1406-12.
- 2 Zanelli E, Huizinga TW, Guerne PA, Vischer TL, Tiercy JM, Verduyn W, *et al.* An extended HLA-DQ-DR haplotype rather than DRB1 alone contributes to RA predisposition. *Immunogenetics* 1998;48:394-401.
- 3 de Vries N, Tijssen H, van Riel PL, van de Putte LB. Reshaping the shared epitope hypothesis: HLA-associated risk for rheumatoid arthritis is encoded by amino acid substitutions at positions 67-74 of the HLA-DRB1 molecule. *Arthritis Rheum* 2002;46:921-8.
- 4 Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.
- 5 Newton JL, Harney SM, Wordsworth BP, Brown MA. A review of the MHC genetics of rheumatoid arthritis. *Genes Immun* 2004;5:151-7.

Authors' reply

We thank Dr Harney and collaborators for their interest and comments on our recent paper.¹ We agree that the use of the relative predispositional effects (RPE) in the comparison of the frequencies of the HLA haplotypes between patients and controls is a valuable method in clarifying the primary and secondary associations.

When dealing with less common haplotypes, and especially when applied to genotype analysis, the statistical power of the method is, however, limited. One possibility would of course have been to classify haplotypes based on the presence of shared epitope and DERA motif, which might have

given a significant protective effect also using the RPE method. We decided primarily to group haplotypes simply based on their increase or decrease among patients without any preassumptions of mechanisms, although we called the haplotype groups susceptibility and protective. This grouping was further used to search for genotype effects and its correlation with the presented models of susceptibility and protection was compared.

Results obtained are far from conclusive but demonstrate lines for further studies still much needed in the field, and we agree with the conclusion that the existence of further major histocompatibility genes influencing RA susceptibility is probable.

S Laivoranta-Nyman, J Ilonen, R Hermann
 Turku Immunology Centre and Department of Virology, University of Turku, Turku, Finland

T Möttönen, A Toivanen
 Department of Medicine, Turku University Central Hospital, Turku, Finland

J Tuokko
 Department of Medical Microbiology, University of Turku, Turku, Finland

R Luukkainen
 Department of Rheumatology, Satalinna Hospital, Satalinna, Finland

M Hakala
 Department of Internal Medicine, University of Oulu, Oulu Finland

P Hannonen
 Department of Medicine, Jyväskylä Central Hospital, Jyväskylä, Finland

M Korpela, U Yli-Kerttula
 Department of Medicine, Tampere University Hospital, Tampere, Finland

Correspondence to: Dr Laivoranta-Nyman; suslai@utu.fi

Reference

- 1 Laivoranta-Nyman S, Möttönen T, Hermann R, Tuokko J, Luukkainen R, Hakala M, *et al.* HLA-DR-DQ haplotypes and genotypes in Finnish patients with rheumatoid arthritis. *Ann Rheum Dis* 2004;63:1406-12.

NSAIDs, including coxibs, probably do more harm than good, and paracetamol is ineffective for hip OA

New EULAR treatment guidelines in hip osteoarthritis (OA) were recently reviewed.¹ The recommendations are allegedly based on top level scientific (grade Ia) data, and advocate the use of paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclo-oxygenase 2 inhibitors (coxibs), in OA of the hip. We interpret the underlying data differently.

The review¹ states that owing to a lack of studies evaluating paracetamol in hip OA alone, recommendations rely on studies that also include OA conditions in other joints. A review of four placebo controlled trials demonstrated an effect size (ES) of 0.21 (95% confidence interval (CI) 0.02 to 0.41).² Two small (n = 50 and n = 60) trials could

Table 1 Relative predispositional effects analysis findings using data from Laivoranta-Nyman *et al.*¹

DRB1-DQA1-DQB1 haplotype	Patients (n = 644)		Controls (n = 1244 haplotypes)		OR	p Value
	No	%*	No	%*		
0401-03-0301	51	7.9	14	1.1	7.6	<10 ⁻¹⁰
0401-03-0302	109	18.4	81	6.6	3.2	<10 ⁻¹⁰
01/10-01-0501	162	33.5	225	19.6	2.1	2×10 ⁻⁹
0408-03-0301	17	5.3	6	0.6	8.5	10 ⁻⁷
0404-03-0302	41	13.4	41	4.5	3.3	6×10 ⁻⁸

OR, odds ratio. p Values are uncorrected.

*The percentages are the percentage of the remaining haplotypes left in the relative predispositional effects analysis at each step, which reduces with each row down the table.

not be pooled for lack of data. Thus, ES calculations are from two trials, where the smallest reported no significant effect, leaving us with a final sample of 387 patients. The EULAR review does not mention that a recent large (n = 779) knee OA trial reported a non-significant effect of paracetamol corresponding to a minuscule 0.8 mm on a visual analogue pain scale (VAS).³ Together, available data clearly demonstrate a lack of effect of paracetamol in large joint OA.

Concomitant with the withdrawal of rofecoxib (Vioxx), and an increasing awareness that other coxibs may also induce serious cardiovascular toxicity, EULAR recommends the use of coxibs as second line treatment after paracetamol for patients at risk for gastrointestinal adverse effects.¹ However, no references to randomised controlled trials (RCTs) or systematic reviews on efficacy are given. To our knowledge only two RCTs have evaluated the use of coxibs in hip OA alone. A trial funded by Pfizer with valdecoxib found a difference over placebo of only 1.6 from a baseline value of 10.8 on the WOMAC subscale of pain,⁴ which corresponds to a modest 7.9 mm on a VAS. Similar results were found for celecoxib in another Pfizer-funded trial.⁵ These results are well below the threshold of 15 mm on a VAS, which defines minimal clinically important differences.⁶ On the other hand, pivotal questions about the safety of coxibs remain unresolved. In our view, this calls for caution and suggests that the use of these drugs should be suspended until comprehensive safety data for all coxibs are available.

The EULAR review states that NSAIDs are effective, but that adverse effects may counter their benefit.¹ This conclusion is based on one systematic Cochrane review,⁷ which allegedly included 14 placebo controlled trials. The ES for pain relief was 0.69 (95% CI 0.12 to 1.26). However, the cited Cochrane review does not include a single study published after 1994. It is not based on 14 placebo controlled trials, but on 14 placebo controlled comparisons. The number of placebo controlled trials included was three (with 9, 146, and 104 patients, respectively) of 2–8 weeks' duration. The given ES of 0.69 was calculated from the results of a single 8 week trial (n = 146),⁸ which reported a mean difference over placebo corresponding to 10 mm on a VAS.

To our knowledge, no further hip-specific RCTs with NSAIDs have been published except the two coxib trials mentioned above, where groups of patients treated with naproxen were included. The efficacy of naproxen in these trials was not significantly different from that of the coxibs. A recent analysis of 23 trials on the efficacy of NSAIDs (including coxibs) in knee OA demonstrated a small effect of treatment on pain corresponding to 10.1 mm on a VAS,⁹ which is too modest to be of any clinical significance in the average patient. No long term trials (>13 weeks) have demonstrated beneficial effects of NSAIDs over placebo in hip or knee OA. Although all NSAIDs may induce serious adverse effects, relevant safety issues cannot be dealt with by short term studies. In our view, it is highly likely that long term use of NSAIDs, including coxibs, does more harm than good in patients with OA of the hip.

We support the EULAR guidelines initiative as a positive contribution to evidence based care of patients with arthritis. However, we believe that some of the recommendations are erroneous and misleading.

In our view, the available information unequivocally demonstrates that standard pharmacological interventions with paracetamol and NSAIDs, including coxibs, cannot be recommended for the osteoarthritic patient.

J M Bjordal, A E Ljunggren, A Klovning, L Sjørdal

Department of Public Health and Primary Health Care, University of Bergen, 5018 Bergen, Norway

Correspondence to: Dr J M Bjordal, jmb@hib.no

References

- 1 Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther K-P et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCIISIT). *Ann Rheum Dis*. Published Online First: 7 October 2004, doi:10.1136/ard.2004.028886.
- 2 Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2004;63: 901–7, doi:10.1136/ard.2003.018531 [published Online First 5 March 2004].
- 3 Miceli-Richard C, Le Bars M, Schmidely N, Dougados M. Paracetamol in osteoarthritis of the knee. *Ann Rheum Dis* 2004;63:923–30.
- 4 Makarowski W, Zhao WW, Bevitt T, Recker DP. Efficacy and safety of the COX-2 specific inhibitor valdecoxib in the management of osteoarthritis of the hip: a randomized, double-blind, placebo-controlled comparison with naproxen. *Osteoarthritis Cartilage* 2002;10:290–6.
- 5 Kivitz AJ, Moskowitz RW, Woods E, Hubbard RC, Verburg KM, Lefkowitz JB, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res* 2001;29:467–79.
- 6 Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient-reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;64:29–33, doi:10.1136/ard.2004.022905 [published Online First 18 June 2004].
- 7 Anonymous. Non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis of the knee Update Software, online or CD-ROM, updated quarterly program. Oxford: The Cochrane Library, 2001, (15 pp, 16 ref, 12 bib.).
- 8 Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. *Arthritis Rheum* 1994;37:529–36.
- 9 Bjordal JM, Ljunggren AE, Klovning A, Sjørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004;329:1317.

Authors' reply

We thank Dr Bjordal for his critical comments on paracetamol and NSAIDs (both conventional and coxibs), which were included in our recent evidence based recommendations for hip osteoarthritis (OA).¹ We agree that direct research evidence for paracetamol in the treatment of hip OA is insufficient as already described in the paper.

Unlike other guidelines, the EULAR evidence based recommendations are generated according to evidence from both clinical expertise and research. We first used a Delphi consensus approach to generate the key clinical propositions for the management of hip OA. We then went on to search systematically for research evidence for these propositions. Paracetamol had been proposed through the Delphi approach, but the research evidence to support its use in hip OA is lacking.

The results were reported to the committee and the strength of recommendation was then determined based both on clinical expertise and research evidence (that is, on all forms of "evidence" in accord with evidence based principles). It is a group decision-making exercise with multidimensional trade-off procedure, taking into account efficacy, side effects, cost effectiveness, logistics of delivery, and patient acceptance and tolerability, not just a simple systematic review of research evidence for efficacy from randomised controlled trials (RCTs) for paracetamol. As a result, paracetamol was still recommended given the evidence from clinical experience (efficacy, safety, availability, etc) and indirect research evidence from knee OA. Not surprisingly, because of this weakness, the strength of recommendation for paracetamol is quite low (table 8 in Zhang et al¹).

We know of the large scale RCT in knee OA,² but this was reported after the EULAR recommendations were submitted. The caveats of that trial and its possible influence on the use of paracetamol have been discussed by us elsewhere.³ Clearly, such data will be included for consideration when we next update the EULAR recommendations.

We appreciate the comments made in relation to NSAIDs, including coxibs, in particular the effect size taken from the Cochrane review,⁴ which was calculated from one trial as you rightly point out. Two other trials funded by Pfizer were not included for assessment because of the strategies of the EULAR Taskforce—evidence will only be included for assessment when a higher grade of evidence is not available. This may be arbitrary but reflects a consensus for the level of evidence, where systematic review is graded as Ia, and allows us to consider not only quality but also the contribution of any single study in the context of the entire literature pool.

As to what should be considered a clinically meaningful improvement, we used effect size as a general outcome in order to cross-compare the treatment programmes. It is suggested that 0.2 is mild, 0.5 is moderate, and over 0.8 is a large clinical effect. Although the threshold of 15% pain reduction may be useful for single programmes, it is less useful for the guideline development, where cross-comparisons between programmes are normally required.

M Doherty, W Zhang
University of Nottingham, UK

Correspondence to: Dr W Zhang, weiya.zhang@nottingham.ac.uk

References

- 1 Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCIISIT). *Ann Rheum Dis*. Published Online First: 7 October 2004, doi:10.1136/ard.2004.028886.
- 2 Miceli-Richard C, Le Bars M, Schmidely N, Dougados M. Paracetamol in osteoarthritis of the knee. *Ann Rheum Dis* 2004;63:923–30.
- 3 Neame R, Zhang W, Doherty M. A historic issue of the Annals: three papers examine paracetamol in osteoarthritis. *Ann Rheum Dis* 2004;63:897–900.
- 4 Towheed T, Shea B, Wells G, Hochberg M. Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2000;(2):CD000517.



NSAIDs, including coxibs, probably do more harm than good, and paracetamol is ineffective for hip OA

J M Bjordal, A E Ljunggren, A Klovning and L Slørdal

Ann Rheum Dis 2005 64: 655-656

Updated information and services can be found at:
<http://ard.bmj.com/content/64/4/655.2>

References

These include:

This article cites 7 articles, 4 of which you can access for free at:
<http://ard.bmj.com/content/64/4/655.2#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>