American College of Rheumatology
Conference Review

Making Education Easy

ACR Annual Scientific Meeting, 24–29 October 2008, San Francisco, USA

In this issue:

Welcome

to the 2008 American College of Rheumatology (ACR) Annual Scientific Meeting, which included a number of presentations on the role of biologic and nonbiologic disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

We begin this review with a look at the ACR's current recommendations for the use of DMARDs in RA. Topics covered in this review include the various roles of methotrexate (MTX), the reduced risk of diabetes among hydroxychloroquine recipients, promising findings from studies involving new investigational agents, and the safety of biologics after rituximab therapy.

Selection and review of the research is carried out independently by Dr Daniel Ching, Consultant Rheumatologist at Timaru Hospital, who attended the 2008 American College of Rheumatology Annual Meeting, held in San Francisco.

I hope you find the Conference Review stimulating reading, and I look forward to receiving your feedback.

Kind Regards,

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Medical Advisor
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ACR 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in RA

Authors: Saag KG et al

Summary: Guidelines and recommendations for the treatment of RA with biologic and nonbiologic therapies are presented in this paper. These extensive, but not comprehensive, guidelines were developed and endorsed by the ACR using a formal group process and based on scientific evidence. Regular updates to the guidelines can be expected to reflect rapidly expanding scientific evidence and changes in practice patterns.

Comment: There have been tremendous advances in the treatment of RA during the past 10 years as a result of new strategies and many new therapies becoming available. There is a need to move proven treatment strategies from trials to the clinic. These ACR recommendations are advisory and not prescriptive as many factors affect our practice besides disease severity, disease duration and the presence or absence of poor prognostic factors. Nevertheless, these are appropriate recommendations for NZ Practice, bearing in mind we only have one biologic (adalimumab) funded for adult RA and one biologic (etanercept) for juvenile idiopathic arthritis (JIA) and adults with a history of JIA. There are few rheumatologists who would agree with all the recommendations, but most of us should agree with the majority of them. They are a reference guide for busy clinicians, and they identify gaps in evidence and provide a framework for future efforts. For those who want to audit their practice, the ACR has developed quality indicators that we can use to improve our practice. These guidelines are complex, but once grasped they would challenge the practice of most rheumatologists.

Reference: Arthritis Rheum (Arthritis Care & Research) 2008; 59(6): 762-84

http://www3.interscience.wiley.com/journal/119635887/abstract

Factors affecting referral and treatment with DMARDs for patients with RA

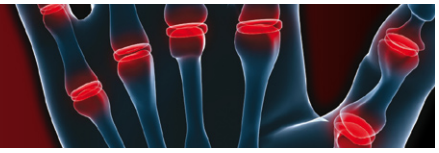
Authors: Reynolds J et al

Summary: In this paper, a random sample of 29 US primary-care physicians were interviewed to identify the factors that influence their decisions to refer patients to a rheumatologist and start DMARD treatment. Most respondents expressed a preference to refer all patients with suspected RA to confirm the diagnosis and initiate treatment, and only 6 indicated that they would start DMARD therapy prior to referral. Many did not feel confident in identifying early-onset RA and were concerned about delays in accessing specialist treatment, and some indicated they would initiate NSAID therapy first if the symptoms were mild. The authors also identified several patient factors (e.g. concerns about DMARDs, preference for natural remedies and travelling to specialist appointments) and system-based factors (e.g. underutilisation of clinical guidelines and drug information sheets).

Comment: I am sure unless a GP had specific training in rheumatology, it is easy for them to miss a diagnosis of RA for osteoarthritis, polymyalgia rheumatica, a traumatic injury, fibromyalgia or some other rheumatic condition in a patient with early RA of insidious onset. Rheumatologists need to do more CME sessions with their referring GPs, orthopaedic surgeons and general physicians. The days of generalists with no specific training in rheumatology managing patients with RA and starting them on DMARDs without referring these patients to a rheumatologist have long gone if patients are not going to be denied optimal treatment for their RA as a result of the dramatic advances during the past 10–12 years.

Which patients should generalists suspect as developing early RA and arrange a rapid referral to a rheumatologist? I have been recommending a simple formula from Emery et al (Ann Rheum Dis 2002; 61(4): 290–7). Rapid referral to a rheumatologist is advised in the event of clinical suspicion of RA, which may be supported by any of the following: 1) ≥3 swollen joints, 2) MTP/MCP involvement (squeeze test positive); or 3) morning stiffness of ≥30 minutes. I have recommended to my referring GPs that they should refer such patients and not wait for results of blood tests or x-rays before deciding whether they would refer. This gets around the problem of some GPs not referring such patients because the ESR is within normal limits or the rheumatoid factor is negative.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 792



An audit of the clinical care of patients with new diagnosed RA in Scotland

Authors: Porter D et al

Summary: This audit of patients with newly diagnosed RA included a comparison of outcomes between two 18-month periods defined as phase 1 (prior to recent advances in RA management; n=251) and phase 2 (which allowed for changes in practice to be instituted; n=230). Findings included ≥1 comorbidity in 63% of patients, 32% had erosive disease at baseline, and the median time from symptom onset to rheumatology referral was 170 days. Disease activity, physical function and health-related quality of life improved during the first treatment year. The most frequently prescribed DMARD was sulfasalazine, while biologic and combination therapies were not commonly used during the first treatment year. The number of methotrexate prescriptions was greater in phase 2 than in phase 1 (23 vs. 6%). The investigators concluded that there was a significant 'performance gap' between outcomes seen in clinical trials and this audit.

Comment: Glasgow is home of the TICORA study, which showed that with tight control (monthly visits) we can achieve low disease activity in a lot of patients with RA and remission in a few patients using traditional DMARDs. This is a multicentre audit of the practice of eight rheumatology units who participated in TICORA and other clinical trials. As Dr Porter said at a poster session, if you ask most rheumatologists, they would say they aggressively increase the treatment of RA until their patients are either in remission or have low disease activity, but this might not be the case in practice, even allowing for some patients who do not want to increase their treatment as much as their rheumatologists. The days of starting sulfasalazine for patients with RA who have poor prognostic factors have gone (see ACR 2008 recommendations on page 1) but interestingly, many rheumatologists in the west of Scotland still use sulfasalazine as their first DMARD in the majority of their patients, which would include those with poor prognostic factors. This is a tradition started in the 1980s when Glasgow was one of three British centres that did the successful original RCT on the use of sulfasalazine in the treatment of RA. Methotrexate was increasingly prescribed in phase 2 of this study (first DMARD used in 6% in phase 1 vs. 23% used in phase 2).

The days of seeing a seropositive, erosive RA patient with active disease and increasing the dose of methotrexate by 2.5 mg/week with a 3-month follow-up are also gone … even if the patients are delighted with this standard of care!

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 1621

All abstracts can be found at http://tinyurl.com/ACRAbstractsOnline, by searching on presentation number on the 'advanced search' page.

About the Reviewer -

Dr Daniel Ching is a Consultant Rheumatologist at Timaru Hospital and is also the Honorary Secretary of the NZ Rheumatology Association.

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In early RA patients with a good initial response to MTX monotherapy continue to have excellent clinical outcomes during the first year of therapy (the SWEFOT study)

Authors: Van Vollenhoven RF et al

Summary: The clinical responses over 1 year among methotrexate monotherapy patients from the SWEFOT study who experienced an 'adequate' initial response to treatment were investigated in this study. Among 487 study participants who received methotrexate at a rapidly escalating dosage up to ≥20 mg/week, 144 responders were continued on methotrexate therapy after 3 months. Treatment was associated with persistent reductions in DAS28 score, with 87%, 79% and 75% with low disease activity at 6, 9 and 12 months, respectively.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 717

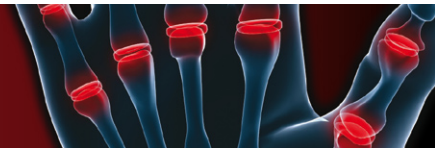
In patients with early RA who fail initial MTX, the addition of anti-TNF yields better ACR and EULAR responses than the addition of conventional DMARDs (the SWEFOT study)

Authors: Van Vollenhoven RF et al

Summary: Two therapeutic strategies for managing patients from the SWEFOT study who did not respond to methotrexate monotherapy (see above) were investigated in this paper. The participants were randomised to one of two treatment arms: A) sulfasalazine plus hydroxychloroquine (or ciclosporin if intolerant), or B) infliximab (or etanercept if intolerant). Significantly more patients in arm B experienced a EULAR good response at 12 months than arm A patients (42% vs. 26%; $p<0.01$). Similarly, patients in arm B experienced greater ACR20, 50 and 70 responses than those in arm A, although the between-group difference for ACR70 was not statistically significant.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 1003

Comment: These abstracts come from Sweden where they have unrestricted access to biologics for their patients with inflammatory rheumatic diseases. They believe it is ethical to show restraint by giving their patients 3–4 months of methotrexate monotherapy before adding another DMARD, whether this is a biologic or nonbiologic DMARD. However, 3–4 months might not be long enough for methotrexate monotherapy to achieve its full potential even if the dose is increased to 25–30 mg/week by 4 months. We can use prognostic factors as in the ACR 2008 recommendations to guide us to treat some subgroups of patients more aggressively, but we all have patients with high levels of rheumatoid factor and anti-CCP antibodies, high tender and swollen joint counts, and/or raised inflammatory indices who are able to achieve remission or low disease state on methotrexate monotherapy. While we can use prognostic factors to guide our initial treatment during the first 6 months for a patient with newly diagnosed RA, it is time we start setting targets that we should aim for with a recognised instrument such as the DAS28 (and there are other simpler instruments) in much the same way as diabetologists use glycosylated haemoglobin values as their targets. This might mean more time assessing patients per follow-up visit for some rheumatologists, but do we really have any choice if we want to translate the advances during the past decade or so into our routine clinical practice? Getting a patient to fill in a functional questionnaire, such as the modified HAQ (Health Assessment Questionnaire) at least once a year, is really a 'no-brainer' because it not only gives us some idea of the patient's function, but it is a way of conveying to the patient we are listening to him/her.



Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders

Authors: Visser K et al

Summary: The systemic review of 304 references has culminated in 10 recommendations for the use of methotrexate in daily clinical practice in accordance with the 3E (evidence, expertise and exchange) initiative. Briefly, these recommendations cover: 1) identification of risk factors for methotrexate toxicity; 2) dosing recommendations; 3) inclusion of folic acid therapy; 4–5) monitoring aminotransferase levels and blood counts, and when to discontinue treatment; 6) long-term therapy; and 7–10) use in combination therapy, with comorbidities, during orthopaedic surgery and during or prior to pregnancy/breastfeeding.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 718

Optimal dosage and route of administration of methotrexate in RA

Authors: Visser K et al

Summary: This systemic review of 39 original articles investigated the optimal dosage regimen for methotrexate in RA. A dose-effect relationship was seen for clinical effect size and toxicity. The authors concluded that their analysis of the evidence suggests that the optimal regimen is a starting dosage of 15 mg/week orally, increasing 5 mg/month until the highest tolerable effective dosage is reached, and a subsequent switch to IM or SC administration if the response is insufficient. They also comment that while 25 mg/week provides good clinical efficacy, toxicity is increased.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 384

Comment: Some NZ rheumatologists participated in the 3E meetings earlier this year for the purpose of developing evidence-based recommendations for the use of methotrexate in daily clinical practice in rheumatic diseases, by integrating evidence and expert opinion by a broad international panel of rheumatologists. The ten recommendations are provided in presentation 718, with their level of evidence and grade of recommendations, to challenge our individual practice

Presentation 384 is also a product of the 3E meetings and concluded that methotrexate should be started at 15 mg/week, increasing by 5 mg/month until the highest tolerable effective dosage with a subsequent switch to SC route if there is insufficient response. My experience tells me there are a number of patients who cannot tolerate methotrexate 15 mg/week. I would still start with traditional 7.5 mg/week during the first 2–4 weeks and then increase the dosage to 15 mg/week. Some patients seem to develop a tolerance for methotrexate, especially if they start on a lower dose, such that their symptoms of nausea and malaise post-methotrexate gradually resolve over a few weeks.

Adalimumab dose escalation improves clinical responses in patients with RA

Authors: Karphouzas GA et al

Summary: The effect of escalating the dosage of adalimumab in patients with RA was explored in this study. Among 48 patients who were receiving adalimumab 40mg every 2 weeks (plus a conventional DMARD), 28 inadequate responders were identified and their adalimumab dosage was increased to 40 mg/week. This increase resulted in new good and moderate EULAR responses in 28.6% and 53.6% of these patients, respectively, and clinical remission (DAS28 <2.6) was achieved in 25% of them. During a median 12-month follow-up period, clinical responses were sustained and no serious adverse events were reported.

Comment: This abstract is of immense interest to NZ rheumatologists. Adalimumab is the only biologic funded by Pharmac for the treatment of RA. For these patients who fail adalimumab 40mg fortnightly, we have nothing else from Pharmac to treat their RA other than corticosteroids. Some rheumatologists are already increasing the dose of adalimumab to 40 mg/week resulting in improved control of some patients' disease. The study provides evidence that this dose escalation can be worthwhile. However, if Pharmac wants us to practice more cost-effective rheumatology, they would do a lot better by funding other biologics than to fund adalimumab 40 mg/week.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 999

Hydroxychloroquine is associated with a reduced risk of diabetes among older adults with RA

Authors: Solomon DH et al

Summary: This analysis included 25,310 older adults with RA and an average exposure to a DMARD or corticosteroid of 91 days (5898 person-years follow-up), of whom 64 had a new diagnosis of diabetes mellitus or had started antidiabetic treatment. Patients who received hydroxychloroquine monotherapy had a lower risk of diabetes than methotrexate monotherapy recipients (hazard ratio [HR] 0.66; 95% CI 0.45, 0.98). Moreover, corticosteroid monotherapy recipients were found to have a dose-dependent increased risk of diabetes (low dose: HR 1.44; 95% CI 1.10, 1.89; high dose: 2.21; 1.63, 2.99), which appeared to counter the reduced risk associated with hydroxychloroquine when both were administered.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 275

Hydroxychloroquine and prediabetes in RA and systemic lupus erythematosus

Authors: Penn SK et al

Summary: The effects of hydroxychloroquine on glucose metabolism and insulin sensitivity were assessed in nondiabetic women with RA (n=177) and SLE (n=149). Women treated with hydroxychloroquine had lower mean glucose levels than those who had not received the agent (86.5 vs. 89.5 mg/dL; p=0.013), although the effect was statistically significant only among women with SLE (p=0.009) and not among those with RA (p=0.092). Median insulin levels were similar. Among women with SLE, hydroxychloroquine recipients had significantly lower homeostasis model assessment index ratio (HOMA-IR) scores than nonrecipients (2.52 vs. 2.87; p=0.048), but these scores did not differ in the women with RA. The authors speculated that insufficient power may be behind the failure to detect hydroxychloroquine-related differences in insulin resistance.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 427

Hydroxychloroquine use reduces risk of diabetes in RA patients

Authors: Bili A et al

Summary: This analysis of data from electronic health records was conducted to verify the previously reported decrease in the incidence of diabetes among patients receiving hydroxychloroquine for RA. During the observation period, 16/525 ever users of hydroxychloroquine were diagnosed with diabetes, compared with 154/1299 never users (incidence rate 17.2 vs. 33.8 per 1000 patient years; p=0.01); the adjusted hazard ratio for diabetes associated with hydroxychloroquine ever use was 0.47 (95% CI 0.26, 0.82; p=0.008).

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 780

Comment: These three abstracts will continue to support hydroxychloroquine as a frequently used treatment among rheumatologists. It is known to have immunomodulatory effects (although weak when used as a monotherapy for RA), some antithrombotic effects, is known to be a relatively safe drug compared with other DMARDs, is cheap and now seems to reduce the risk of diabetes in patients with RA and SLE who are already at increased risk of cardiovascular events by the nature of their inflammatory rheumatic diseases. Most patients with SLE should be on hydroxychloroquine unless there are contraindications.

All abstracts can be found at http://tinyurl.com/ACRAbstractsOnline, by searching on presentation number on the 'advanced search' page.

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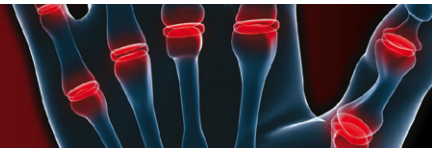

CP-690,550, an oral JAK inhibitor, is a well-tolerated and effective long-term treatment for patients with moderate to severe RA

Authors: Silverfield J et al

Summary: This open-label study investigated the efficacy and safety of CP-690,550, an oral Janus kinase-3 (JAK-3) inhibitor, in 129 patients who received 5mg of the agent twice daily for ≤6 months (median treatment duration 109 days). Mean DAS28 scores were 3.60 and 3.47 at months 1 and 6, respectively, with 5 patients discontinuing treatment due to lack of efficacy. There were 93 mild, 64 moderate and 3 severe adverse events. The investigators concluded that CP-690,550 is well tolerated and effective over 6 months for the treatment of patients with moderate-to-severe RA.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 716

Treatment of RA with a Syk kinase inhibitor

Authors: Weinblatt ME et al

Summary: In this phase II RCT, 189 patients receiving chronic methotrexate therapy for active RA were enrolled and treated with the Syk kinase inhibitor, R788, twice daily with an ascending dose schedule (50, 100 and 150mg). ACR20 response rates at week 12 (primary endpoint) were 65% and 72% for R788 doses of 100 and 150mg, respectively, compared with 38% and 32% for placebo and the 50-mg R788 dose, respectively ($p=0.008$ for 100mg and $p<0.001$ for 150mg). Similar findings were seen for ACR50 and ACR70 response rates and DAS remission rates. Diarrhoea and neutropenia were the major adverse events, but were dose related and reversible.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 1189

Comment: These two abstracts herald a possible new era in the treatment of RA, transitioning from systemically administered proteins with current biologics to small molecules that modulate transcription factors and signalling pathways. These agents are given orally unlike current biologics, which have to be administered parenterally. They might therefore be potentially more cost effective than current TNF inhibitors and other biologics. However, it will be at least a few years before they can be shown to be as effective as current biologics with an acceptable toxicity profile.

Long term safety of rituximab: 6-year follow-up of RA for clinical trials and re-treatment population

Authors: van Vollenhoven FR et al

Summary: This pooled analysis of long-term data from clinical trials investigating rituximab in RA involved 2578 patients (5013 patient-years) who had received ≥2 courses of the agent (133 received ≥5 courses). Infusion-related reactions occurred in 35% of the patients, of which <1% were classified as serious. The rates for overall and serious adverse events and overall infection events remained stable for each treatment course (1–5). The rate of serious infections associated with treatment course 5 was higher than it was for courses 1–4 (6.83 vs. 3.79–4.84 per 100 patient-years), but the authors comment that this finding needs to be interpreted with caution due to the relatively low number of patients who received a fifth course.

Comment: Rituximab can be potentially cheaper than TNF-α inhibitors for the treatment of RA especially as some of these patients respond so well after the first two courses (given in two doses over a fortnight, 6 months apart) that they don't need retreatment for 9–12 months, and even longer. There have been concerns expressed about the effects of long term B-cell maturation inhibition, and this abstract is reassuring about the long-term safety of rituximab.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 361

Is it safe to use biologics after rituximab therapy?

Authors: Singh V et al

Summary: The safety of the use of abatacept, adalimumab, etanercept and infliximab in a cohort of 22 patients with RA who had previously failed treatment with rituximab, and also failed biologic therapy prior to rituximab, was explored in this study. The incidence of serious adverse events did not increase after the re-initiation of biologic therapy. Minor adverse events occurred more often in patients who received abatacept (after failing rituximab therapy), but none resulted in hospitalisation.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation F107

Safety of other biologic therapies following rituximab treatment in RA patients

Authors: Genovese M et al

Summary: This second paper investigating the safety of biologic agents after rituximab therapy investigated serious infection rates in 185 patients. Prior to initiation of biologic treatment, most of the patients had depleted CD-19 B-cell counts. The rates of serious infection events prior to biologic therapy (during rituximab treatment) and after initiation of biologic therapy were 6.99 and 5.49 events/100 patient-years, respectively. The authors commented that the infections reported were variable and typical for patients with RA.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation 1671

Comment: There have been theoretical concerns that patients who fail rituximab for the treatment of RA are at increased risk of infections if they are subsequently given a biologic while their CD-19 B-cell counts are still low. It can take over a year for the B-cells to recover. These two abstracts show there is no significantly increased risk of adverse effects, including serious infection events, when other biologics are given even when the CD-19 B-cell counts are still low.

Efficacy and safety of rituximab in patients with moderately to severely active SLE (the EXPLORER study)

Authors: Merrill JT et al

Summary: This phase II/III study investigated the efficacy and safety of rituximab in 257 patients with moderately to severely active extrarenal SLE randomised to receive rituximab 1000mg or placebo on days 1, 15, 168 and 182. There were no significant differences between the rituximab and placebo groups for any of the primary (major, partial and no clinical responses) or secondary endpoints. The rates of serious adverse events were 37.9% and 36.4% for the rituximab and placebo recipients, respectively, although all four patients who experienced serum sickness syndrome were from the rituximab group.

Comment: The best way to comment on this abstract is to relate what happened during the question time following the presentation. A member of the audience asked: "Is rituximab now considered an obsolete treatment for SLE?" Dr Merrill answered this by asking the room full of attendees to put their hands if they have used rituximab for the treatment of moderately to severely active SLE. Approximately half the audience put their hands up. She then asked if any of them would now stop using rituximab for patients with SLE. No one put their hands up! Although this study is negative, the jury is still out on the use of rituximab for the treatment of SLE. Meanwhile, I expect it will continue to be used in view of the number of positive reports of its efficacy for the treatment of SLE, while we don't have much therapeutic choice for patients with moderately to severely active extrarenal disease that is resistant to antimalarials and corticosteroids.

Reference: ACR/ARHP Annual Scientific Meeting, San Francisco, USA, October 2008; Presentation L12

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