Rheumatology 2009;48:440–454

Letters to the Editor

Rheumatology 2009;48:440–441
doi:10.1093/rheumatology/ken491
Advance Access publication 19 January 2009

Safety of combination therapy with rituximab and etanercept for patients with rheumatoid arthritis

Sir, Treatment of RA with rituximab (RTX) is established for patients with an inadequate response to anti-TNF-α therapy [1–3]. Previous RTX trials show an ACR-70 response in ~15% of all patients after 24 weeks [2, 3]. Therefore, a significant fraction of RA patients cannot be treated sufficiently. Other trials showed that combinations of etanercept (ETN) and anakinra [4] or ETN and abatacept [5] were associated with severe infections and are not recommended. Current guidelines propose that patients with an inadequate response to one or more anti-TNF-α drugs should switch to RTX therapy [6]. Recently published data suggest a switch to RTX after inefficacy of the first anti-TNF-α drug [7]. Current practice for switching to RTX is to discontinue ETN for 2 weeks, adalimumab (ADA) for 4 weeks and infliximab for 4–8 weeks before RTX therapy. However, it is not clear whether this is necessary to prevent infections or whether discontinuation leads to disease exacerbation.

We describe a retrospective analysis of 18 consecutively selected patients with long-standing active RA according to the ACR 1987 classification criteria who received RTX therapy. The pro and contra for combination therapy was discussed with the patient and an informed patient consent was obtained for this study. Patients were previously treated with up to six DMARDs and three anti-TNF-α drugs, but still had significant disease activity. Patients were mostly treated with MTX, LEF or MTX + LEF in combination with ETN or ADA. Anti-TNF-α drugs were discontinued and 2 weeks later RTX therapy was initiated with two infusions of 1 g within 2 weeks. Pre-medication with 100 mg prednisone was used to prevent anaphylactoid reactions. Concomitant DMARDs were not changed. During the follow-up period intra-articular steroid injections and oral pulses with up to 40 mg prednisone were offered to patients with active synovitis. Follow-up visits were scheduled 4 and 8 months after the first RTX infusion or earlier if necessary. Two months after the first RTX infusion six patients did not achieve a satisfying clinical response and had persistently high CRP and ESR parameters. Results from the REFLEX study showed that the clinical benefit of RTX appears ~4 weeks after the first infusion with a DAS-28 improvement of −1.6 after 4 weeks and −1.8 after 12 weeks [3]. Therefore, these six patients re-started anti-TNF-α therapy with ETN, which corresponds to an RTX + ETN combination because of the long-lasting depletion of B cells [8, 9]. ETN was used because of its short half-life and concerns about infections. After 2 months of RTX + ETN (4 months after the first RTX infusion) all clinical and serological parameters improved significantly. All patients gradually improved between 4 and 8 months. The second RTX cycle was started in both groups after re-occurrence of disease activity after ~8 months. Patients who received a longer duration of previous anti-TNF-α therapies (Table 1). Clinical parameters were not different in both groups at the time of the first RTX infusion. Inflammatory parameters were higher in the RTX + ETN group, which correlates to the selection procedure of these patients.

We were concerned about infections in patients receiving RTX + ETN. The six patients were exposed to RTX + ETN for a mean of 18.5 months and overall 111 patient-months, respectively. No serious infections requiring an i.v. therapy or hospitalization were observed up to now (October 2008). One non-serious infection occurred in a patient in the RTX + ETN group, who had a re-exacerbation of perioral herpes simplex. The doses of LEF and prednisone were reduced and the lesions rapidly resolved. A second patient had suffered from frequent mild respiratory infections in the past which did not exacerbate during RTX + ETN therapy. A third patient received total finger joint...
replacement 2 yrs before and some protheses had to be explanted in the past because of infection. We did not observe an infection of the remaining devices during RTX + ETN therapy.

Depletion of B cells and anti-TNF-α therapy target different pathways of inflammation and therefore probably act synergistically. TNF-α is one of the most powerful pro-inflammatory cytokines and is produced by monocytes, RTX treatment virtually depletes B cells in the circulation, but synovial B cells are only depleted in patients with RA who show a good response to RTX therapy [10]. An inflammatory network with multiple cell types, cytokines and chemokines contributes to synovitis. Elimination of one specific mediator might be bypassed by other mechanisms.

This is the first report which shows that the combination of RTX + ETN and DMARDs might be safe and effective in patients with RA.

### Rheumatology key message

- Combination of RTX and ETN is safe and effective in patients with RA.

### Disclosure statement

R.M. has received financial/material support from Wyeth and Roche (less than 5000 Euro). H.-M.L. has received grants/research support from Abbott, MSD, Sanofi-Aventis, Roche, Wyeth, Bristol Myers Squibb, Novartis, Essex (less than 5000 Euro each). N.B. was supported by Wyeth and Roche (less than 5000 Euro each). All other authors have declared no conflicts of interest.

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Accepted 3 December 2008

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**The use of fish oil in the community: results of a population-based study**

Sir, Fish oil has been demonstrated to have symptomatic benefits [1] and improve disease activity in RA [2]. In addition, fish oil has been shown to have NSAID-sparing effect in patients with RA [3–6]. Recently, the use of fish oil in patients with early RA has been shown to reduce cardiovascular risk factors in these patients already at increased risk of cardiovascular disease [6]. In addition, reduction in NSAID use is likely to reduce cardiovascular and gastrointestinal harm in these patients. A previous study of complementary medicine use in outpatients with OA showed 5% were taking fish oil supplements [7]. Fish oil is widely marketed to the general public for joint and general health benefits. We undertook this population-based study to determine how the use of fish oil and its effects in the community.

Participants of the North West Adelaide Health Study (NWABS) were recruited from households randomly selected from the electronic telephone directory in 2000–02. At follow-up of the NWABS cohort in 2004–05 (response rate: 81.0%), clinic assessment and medication data were available on 3161 individuals. Respondents completed surveys and clinic assessment included measurement of blood pressure, medication use (including fish oil and NSAIDs), information-assessing doctor-diagnosed conditions [including arthritis (OA, RA, other), osteoporosis, diabetes, asthma and cardiovascular disease (myocardial infarct, angina, stroke, transient ischaemic attack)], joint pain (in at least one of the following sites—foot, knee, hip, hand, shoulder) and behavioural risk factors, health service utilization and demographics. These methods have been previously described [8].

Data were weighted to Census data by region, age group, gender and probability of selection in the household, to provide population-representative estimates. Data were analysed using SPSS (Version 15.0, SPSS, Chicago, IL, USA). Multivariable logistic regression analysis determined the likelihood of fish oil use associated with arthritis adjusted for covariates including age, smoking status, education level and income. The study was approved by the institutional ethics committees of the North West Adelaide Health Service, and all subjects gave written informed consent.

Overall, among participants who were able to provide information related to their medication use, 6.0% reported that they took fish oil. The overall prevalence of self-reported arthritis was 21.4%, including self-reported prevalence of OA (7.5%), RA (2.9%) and other (11%). Those reporting that they had RA reported the highest level of taking fish oil (18.8%), followed by those with OA (13.7%). Overall, 42.4% of those taking fish oil were using it for ‘General health and wellbeing’ and 32.6% for ‘Joint pain or joint health’. Of the 274 participants in whom doses of fish oil were available, the median daily dose was 1 g (range 0.2–20 g). Only two participants were taking liquid fish oil, the remainder were taking fish oil in capsule form.

Fish oil use was independently associated with female gender, increasing age and increasing household income, but not with higher educational attainment (Table 1). Participants with doctor-diagnosed arthritis were more likely to use fish oil, compared with those without joint pain and those with joint pain without arthritis diagnosed by a doctor. Those with history of cardiovascular disease, uncontrolled hypertension and those using NSAIDs were less likely to use fish oil, although these associations were non-significant. Former and non-smokers were more likely to use fish oil than smokers. Participants using fish oil were significantly more likely to have had frequent visits to their general practitioner and alternative therapists than those not taking fish oil.

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