RHEUMATOLOGY

Letters to the Editor

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Improvement in cardiovascular biomarkers sustained at 4 years following an initial treat-to-target strategy in early rheumatoid arthritis

Rheumatology key message

- Initial treat-to-target therapy in early rheumatoid arthritis has sustained cardiovascular risk benefits at 4 years.

SIR. It is well recognized that individuals with RA are at greater risk of cardiovascular disease (CVD), with EULAR guidance advising optimal control of disease activity to reduce this risk [1]. The cardiovascular substudy of the Infliximab as Induction Therapy in Early Rheumatoid Arthritis (IDEA) trial evaluated infliximab (IFX) + MTX *vs* MTX + methylprednisolone (MP) ($n = 38$ and 41 in each group, respectively) using a treat-to-target approach in early RA and reported improvements in soluble cardiovascular biomarkers in both groups at week 78, with a greater improvement in insulin resistance in the IFX + MTX group [2, 3]. At week 78 the patients were discharged back to routine clinical care. Four years after their initial baseline IDEA visit, they were invited to participate in a follow-up study (IACON REC 09/H1307/98) to determine any long-term cardiovascular benefits of treat-to-target management and to evaluate for differences between the initial IFX + MTX and MTX + MP treatment arms.

Following obtaining informed consent, patients were assessed for RA disease activity and medication use and any new diagnosis of ischaemic heart disease (IHD), cerebrovascular accidents (CVAs), peripheral arterial disease (PAD), hypertension, hypercholesterolaemia or diabetes mellitus (following medical notes review/patient questioning). Mirroring our previous IDEA substudy, blood samples were taken to quantify three commonly measured soluble cardiovascular biomarkers: N-terminal pro-brain natriuretic peptide (NT-proBNP), homeostasis model assessment–estimated insulin resistance (HOMA-IR) and total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C).

Eighteen patients were lost to follow-up between week 78 and year 4 (IFX + MTX, $n = 10$; MTX + MP, $n = 8$); follow-up data were available for 28 in the IFX + MTX group and 33 in the MTX + MP group. Comparing IFX + MTX *vs* MTX + MP at the baseline visit of the IDEA study, 64 *vs* 70% were female, 54 *vs* 64% were RF positive and 63 *vs* 78% were ACPA positive, respectively.

At year 4, of those initially in the IFX + MTX group, the three-variable 28-joint DAS (DAS28) was 1.80 (95% CI 1.10, 2.50), none were receiving oral steroids, 75% were receiving conventional synthetic DMARDs (csDMARDs; 61% MTX monotherapy) alone and 25% were receiving biologic DMARDs [bDMARDs; 18% TNF inhibitor (TNFi) therapy; 12% IFX], compared with those initially in the MTX + MP group, where the three-variable DAS28 was 1.9 (95% CI 1.1, 2.35), 9% were receiving oral prednisolone (median dose 5 mg), 73% were receiving csDMARDs (36% MTX monotherapy) alone and 18% were receiving bDMARDs (15% TNFi therapy, 12% IFX).

Since week 78, there were five new diagnoses of cardiovascular disease (IFX + MTX: 2 IHD, 1 CVA; MTX + MP: 1 IHD, 1 PAD), no new diagnoses of diabetes mellitus and seven new diagnoses of hypercholesterolaemia (IFX + MTX, $n = 4$; MTX + MP, $n = 3$). One (4%) of the IFX + MTX cohort received a new diagnosis of hypertension compared with six (18%) of the MTX + MP cohort ($P = 0.225$).

Soluble biomarker data were available for 40 patients (IFX + MTX, $n = 20$; MTX + MP, $n = 20$). Results at weeks 26 and 78 were comparable to those of the original IDEA cardiovascular substudy [2]. Continued improvements in soluble biomarkers of cardiovascular risk 4 years from baseline were shown regardless of the drug regimen (see Table 1); NT-proBNP values were 53–69% of baseline, HOMA-IR were 45–57% of baseline and TC/HDL-C decreased by 1.28–1.61. There were no significant differences observed between the treatment groups at year 4.

While the difference in the incidence of new hypertension did not reach statistical significance, and notably some patients in the MTX + MP group were taking oral prednisolone at year 4, it may be clinically important. While glucocorticoids have a known association with hypertensive disease [4], IFX has been linked with reduced systolic blood pressure in patients with RA. In a trial of 16 RA patients, new IFX exposure was associated with a reduction in systolic blood pressure, along with reductions in plasma norepinephrine and renin activity [5]. This could suggest that the mechanism extends beyond that of simply reducing disease activity and inflammation.

Our cross-sectional analysis may also suggest that the initial beneficial impact of IFX + MTX on insulin resistance shown at week 78 had been lost by 4 years. However, the findings are limited by the small sample size and cross-sectional nature of the analysis, with a lack of knowledge about fluctuating disease activity/inflammation over the last 30 months—a known confounder of HOMA-IR [6]. In addition to patients receiving oral steroids at year 4 in the MTX + MP group, not all patients remained on IFX after week 78 in the alternative arm. Perhaps, for sustained insulin resistance improvement, continuous exposure to the drug is required.

To conclude, we report an intensive 78 week treat-to-target programme in early RA is associated with sustained

Table 1 Changes to biomarker and lipoprotein values over time, separated by treatment regimen

Change in variable	MTX + MP	IFX + MTX	Unadjusted difference (95% CI), *P*-value	Adjusted difference (95% CI), *P*-value[b]
Week 26				
NT-proBNP mean ratio	0.88 (n=30)	0.95 (n=26) (0.96)[a]	1.09 (0.77, 1.54), 0.636[c] 1.10 (0.77, 1.57), 0.610[a,c]	1.11 (0.78, 1.59), 0.548[c] 1.14 (0.80, 1.61), 0.456[a,c]
HOMA-IR mean ratio	0.67 (n=30) (0.74)[a]	0.67 (n=25)	1.00 (0.57, 1.77), 0.990[c] 0.91 (0.53, 1.56), 0.725[a,c]	0.77 (0.50, 1.20), 0.244[c] 0.74 (0.50, 1.11), 0.145[a,c]
TC/HDL-C mean	−0.64 (n=30)	−0.82 (n=26)	−0.18 (−0.88, 0.52), 0.619	−0.21 (−0.78, 0.37), 0.472
Week 78				
NT-proBNP mean ratio	0.79 (n=30)	0.91 (n=22) (0.91)[a]	1.15 (0.75, 1.77), 0.517[c] 1.14 (0.74, 1.79), 0.529[a,c]	1.17 (0.76, 1.82), 0.473[c] 1.13 (0.75, 1.72), 0.550[a,c]
HOMA-IR mean ratio	0.81 (n=30) (0.89)[a]	0.66 (n=22)	0.81 (0.44, 1.51), 0.506[c] 0.74 (0.41, 1.33), 0.303[a,c]	0.64 (0.39, 1.06), 0.08[c] 0.62 (0.38, 0.098), 0.042[a,c]
TC/HDL-C mean	−0.94 (n=29)	−1.13 (n=21)	−0.19 (−1.08, 0.69), 0.663	−0.12 (−0.75, 0.51), 0.701
Year 4				
NT-proBNP mean ratio	0.53 (n=20)	0.69 (n=20) (0.69)[a]	1.31 (0.74, 2.31), 0.342[c] 1.32 (0.73, 2.36), 0.346[a,c]	1.32 (0.73, 2.37), 0.350[c] 1. 31 (0.72, 2.38), 0.368[a,c]
HOMA-IR mean ratio	0.45 (n=20) (0.52)[a]	0.57 (n=20)	1.26 (0.67, 2.37), 0.471[c] 1.09 (0.61, 1.95), 0.765[a,c]	0.91 (0.58, 1.44), 0.679[c] 0.83 (0.59, 1.17), 0.272[a,c]
TC/HDL-C mean	−1.28 (n=20)	−1.61 (n=20)	−0.33 (−1.45, 0.78), 0.551	−0.47(−1.061, 0.122), 0.116
HDL-C mean (S.D.), (mg/dl)	11.6 (14.0) (n=20)	18.0 (11.7) (n=20)	6.4 (−1.8, 14.7), 0.125	6.8 (−1.2, 14.7), 0.093
LDL-C mean (S.D.), (mg/dl)	22.2 (28.2) (n=20)	5.9 (41.5) (n=20)	−16.3 (−39.0, 6.4), 0.155	−12.3 (−31.0, 6.4), 0.190
ApoA mean (S.D.), (g/l)	−0.025 (0.365) (n=20)	−0.018 (0.192) (n=20)	0.007 (−0.180, 0.193), 0.944	0.032 (−0.131, 0.195), 0.694
ApoB mean (S.D.), (g/l)	0.255 (0.159) (n=20)	0.187 (0.251) (n=20)	−0.069 (−0.204, 0.067), 0.310	−0.062 (−0.188, 0.063), 0.320
LpA, geometric mean, (g/l)	0.889 (n=16)	0.938 (n=15)	1.05 (0.72, 1.55), 0.777[c]	1.03 (0.69, 1.53), 0.887[c]

[a]Minus extreme outlier. [b]Adjusted for baseline values. [c]Values exponentiated to give the ratio of the difference of one group *vs* another with associated CIs. *$P < 0.05$. ApoA: apolipoprotein A; ApoB: apolipoprotein B; LDL: low-density lipoprotein cholesterol; LpA: lipoprotein A.

long-term benefit in the improvement of soluble biomarkers of CVD, suggesting the potential for a reduction of cardiovascular risk in the long term.

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Isabel Mortimer[1,2], Lesley-Anne Bissell[1,2], Elizabeth M. A. Hensor[1,2], Lukasz Kozera[1,2], Sarah L. Mackie[1,2], Agata N. Burska[1,2], Jackie L. Nam[1,2], Helen Keen[1,2], Edith Villeneuve[1,2], Helena Donica[3], Maya H. Buch[1,2], Philip G. Conaghan[1,2], Paul Emery[1,2], Ann W. Morgan[4] and Jacqueline Andrews[1,2]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, [2]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [3]Department of Biochemical Diagnostics, Medical University

of Lublin, Lublin, Poland and [4]*Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK*
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Correspondence to: Jacqueline Andrews, Chapel Allerton Hospital, Leeds Teaching Hospitals NHS Trust, Chapeltown Road, Leeds LS7 4SA, UK. E-mail: j.andrews@leeds.ac.uk

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Long-term preservation of measles and rubella specific-IgG antibodies in children with enthesitis related arthritis on anti-TNFα treatment: a prospective controlled study

Rheumatology key message

- Enthesitis related arthritis children on antiTNFa show accelerated measles and rubella antibody loss while retaining satisfactory seroprotection.

Sir, Immunization in patients with rheumatic disease is essential, as they are at risk for infection due to the immunosuppressive effect of both the disease and its treatment. Data regarding response and long-term immunological memory to specific vaccines are lacking. At present, we are experiencing major measles outbreaks throughout Europe. Measles infection is associated with potentially serious complications [1] as well as sustained immune-memory loss predisposing patients to bacterial/opportunistic infections [2]. On the other hand, rubella infection in pregnant women is linked to serious neonatal consequences [1].

In this study we aimed to determine the immune status against measles and rubella in previously vaccinated enthesitis related arthritis (ERA) patients, prior to the commencement of biologic (anti-TNFα) treatment and at one and three years later and compare these findings to healthy controls. Secondary outcomes were to assess if additional treatment would further interfere with seroprotection rates and antibody status.

This was a prospective, controlled study held at P. & A. Kyriakou Children's Hospital over a period of six years. Forty-one ERA patients fulfilling the ILAR JIA classification criteria [3] and 149 controls were included. All participants had received two doses of MMR vaccine at 2 and 5 years of age. Blood sampling was performed prior to initiation of anti-TNFa treatment and at specific intervals afterwards (0, 12, 36 months). In the majority of patients, biologic and synthetic DMARDs were initiated simultaneously following failure of NSAID treatment. Mean time from diagnosis to anti-TNFα treatment was 9.4 months; mean duration of treatment was 3.4 years. Seroprotection rates as well as measles and rubella-IgG titres were measured; titres were assessed by ELISA and were expressed as geometric mean concentrations (GMCs). Commercial EIA kits for detection of antibodies against MMR (Dade-Behring, Germany) were used. The cut-off value for seroprotection was deemed at 120 IU/ml (measles) and 10 IU/ml (rubella), based on international standards [4]. Total IgG levels were measured simultaneously.

All participants were included and sampled between November 2011 and July 2018. The study was performed in compliance with the Declaration of Helsinki. The Hospital's Research and Ethics' Committee approved the study (Approval number 19/2045/11–08-2011); informed consent was obtained. Statistical significance was set at $P < 0.05$ and analyses were conducted using STATA (version 13.0).

ERA patients were less up to date with their vaccinations ($P = 0.02$). Seroprotection rates were adequate for both the ERA and the control group. Nonetheless, the ERA group had consistently, but not statistically significant, lower rates. Mean measles-IgG antibodies (as well as GMCs) were significantly lower in the ERA compared with the control group ($P < 0.05$) at 1 and 3 years' follow-up, but not at diagnosis. The same was also evident for rubella to a more pronounced degree ($P < 0.01$) (Table 1). None of the participants had hypogammaglobulinaemia at the time of blood sampling. None of the participants were infected by rubella or measles during the study period. During the follow-up period, the ERA group had greater decrease in antibody levels as indicated from the significant interaction effect of analysis (both measles and rubella). Subgroup analysis showed that age, gender, time interval between the two doses of the vaccine as well as time lapse from last MMR vaccination to initiation of treatment did not affect either rubella or measles-specific-IgG concentrations. Intermittent systemic corticosteroid