Infliximab is Associated with Improvement in Arterial Stiffness in Patients with Early Rheumatoid Arthritis — A Randomized Trial

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ABSTRACT. ***Objective.*** To determine the efficacy of methotrexate (MTX) with infliximab (IFX) compared with MTX alone in the prevention of atherosclerosis and arterial stiffness in patients with early rheumatoid arthritis (RA).

Methods. A randomized, open-label study in which early RA patients with active disease were treated with MTX alone (n = 20) and MTX plus IFX (n = 20) for 6 months. Patients were assessed every 3 months. Patients from the MTX-alone group who failed to achieve 28-joint Disease Activity Score remission (DAS28 ≤ 2.6) at 6 months were permitted to escape to open-label IFX. Intima-media thickness (IMT), pulse wave velocity (PWV), and augmentation index (AIx) were measured at baseline, 6 months, and 12 months.

Results. At 6 months, there was a significantly greater reduction in PWV in the MTX-alone group (0.18 ± 1.59 m/s) compared with the MTX plus IFX group (–0.78 ± 1.13 m/s; p = 0.044), accompanied by significantly greater reduction in patient's global assessment, number of swollen joints, C-reactive protein, and DAS28 in the MTX plus IFX group compared to the MTX-alone group. The changes in IMT and AIx were similar between the 2 groups. At 12 months, there was a trend favoring early combination treatment with regard to the reduction in PWV (p = 0.06).

Conclusion. MTX plus IFX causes a more significant reduction in PWV than MTX alone in patients with early RA after 6-month treatment, and further improvement may be achieved in patients who continued on longterm tumor necrosis factor-α blockers, suggesting that early, effective suppression of inflammation may prevent progression of atherosclerosis by improving vascular function. (First Release Sept 15 2012; J Rheumatol 2012;39:2267–75; doi:10.3899/jrheum.120541)

Key Indexing Terms:
INFLIXIMAB INTIMA-MEDIA THICKNESS PULSE WAVE VELOCITY
AUGMENTATION INDEX EARLY RHEUMATOID ARTHRITIS RANDOMIZED TRIAL

Patients with rheumatoid arthritis (RA) die prematurely compared with the general population[1], primarily because of cardiovascular (CV) disease[1,2]. Evidence suggests that this phenomenon also occurs in patients with early RA[3,4,5]. Chronic inflammation is probably a driving force for premature atherosclerosis in RA[6]. One study suggested that the pathogenic processes of atherosclerosis may be in place even before a diagnosis of RA[7]. Evidence of subclinical atherosclerosis including increased intima-media thickness (IMT), carotid atherosclerotic plaque, and arterial stiffness has been observed in RA patients with recent disease onset in some[8,9,10,11,12] but not all studies[13,14,15], suggesting that

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the accelerated atherogenic process related to inflammation may precede symptom onset.

Data from observational studies have demonstrated that anti-tumor necrosis factor (TNF) therapy may decrease the risk of new CV events[16,17], thus potentially reducing overall mortality. On the other hand, no significant association between exposure to anti-TNF treatment and the risk of experiencing a first acute coronary syndrome was observed in patients who received TNF inhibitor therapy within the first few years following the diagnosis of RA[18]. The use of surrogate endpoints instead of actual CV events may provide more evidence on whether patients with RA may benefit from potent antiinflammatory treatment such as anti-TNF therapy for the prevention of premature atherosclerosis. Data are inconsistent from observational studies regarding the effects of TNF blockers on atherosclerosis and arterial stiffness in patients with established RA[19]. The posthoc analysis of the first randomized controlled study (RCT) showed that pulse wave velocity (PWV) improved in patients with RA after treatment with infliximab (IFX) for 56 weeks[20]. However, the placebo-controlled part of the study was unable to assess vascular effects of IFX because of early drop-out of the placebo group. Another recent RCT demonstrated that biologics monotherapy improved arterial stiffness in patients taking methotrexate (MTX) or biologically naive patients with early RA[21]. However, whether disease-modifying antirheumatic drugs (DMARD) alone may result in a similar degree of change remained uncertain. Data from the BeSt study have demonstrated that initial combination therapy with MTX and IFX seemed to provide earlier clinical improvement and less progression of joint damage compared to step-up combination therapy[22]. Whether early control of inflammation using combination therapy with MTX and IFX results in less progression of vascular damage compared to delayed IFX treatment in the long term would also be of interest.

We first compared the efficacy of MTX with and without IFX in improving IMT and arterial stiffness in patients with early RA over a period of 24 weeks. Second, we assessed the differences in the progression of atherosclerosis and vascular stiffness over a period of 1 year between patients who received early versus delayed IFX treatment.

MATERIALS AND METHODS

Trial design. This was a prospective, randomized, open-label, single-center pilot study. Patients were age 18 years or older, with a diagnosis of active RA as defined by the American College of Rheumatology 1987 revised criteria[23], and a disease duration not less than 2 years. This included patients with at least 4 swollen and tender joints, 28-joint Disease Activity Score[24] C-reactive protein (DAS28/CRP) > 3.2, and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or CRP ≥ 10 mg/l.

Patients were ineligible if they had contraindications to treatment with MTX or IFX. Patients were also ineligible if they had a history of overt CV diseases or if they had been treated with aspirin, angiotensin-converting enzyme inhibitors, statins, or prednisolone > 10 mg daily, or had previous treatment with IFX or other biological agents.

Study protocol. Forty patients with early RA were recruited. Patients were examined clinically at Weeks 0, 2, 6, and every 8 weeks thereafter until the end of the study, which included clinical examination and laboratory tests. Carotid ultrasound, PWV, and pulse wave analysis (PWA) were performed at baseline, 6 months, and 12 months. The Clinical Research Ethics Committee of the Chinese University of Hong Kong approved the study protocol, and informed consent was obtained from all patients.

The 40 patients were randomly assigned to receive either MTX alone (n = 20) or combination IFX plus MTX (n = 20).

Clinical interview. All patients were interviewed and examined with the use of standardized data collection instruments. At baseline, we quantified extent of disease by recording extraarticular manifestations; previous treatment was recorded by patient interview and chart review. Other data including smoking habits and medical history were noted. DAS28 was determined at each visit, and patients were asked to fill in the Health Assessment Questionnaire (HAQ)[25]. Anthropomorphic measurements include height and weight, 2 consecutive blood pressure (BP) readings in sitting position, and heart rate.

Treatment protocol. Adjustment of treatment was made according to the protocol below if patients could not achieve remission (defined as DAS28 ≤ 2.6).

For both groups, MTX was started at a dose of 7.5 mg/week and gradually titrated up to 15 mg/week by Week 4 (increment of 2.5 mg/wk) and maintained at the same dose until the end of the study. If remission was not achieved by Week 14, the MTX dose was increased gradually to 20 mg/week by Week 20.

Patients in the IFX + MTX group received IFX 3 mg/kg at Weeks 0, 2, 6, and every 8 weeks thereafter. For patients who did not achieve remission, IFX was increased to 5 mg/kg by Week 22 and 10 mg/kg by Week 38 until the end of the study.

Patients in the MTX-alone group who failed to achieve remission by Week 22 were allowed to receive IFX 3 mg/kg at Weeks 24, 26, 30, and every 8 weeks thereafter. At Week 38, the dosage of IFX was increased to 5 mg/kg and then 10 mg/kg by Week 46 if remission was not achieved.

Laboratory tests. These tests were done every 3 months: complete blood count, liver and renal function, ESR, CRP, fasting blood glucose, and lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides).

Carotid intima-media thickness (IMT) and plaque. Carotid IMT was measured using a high-resolution B-mode ultrasound machine (iE33, Philips). Briefly, duplex carotid ultrasound was performed by an experienced cardiologist (QS) using an 11-MHz linear vascular probe. IMT was measured offline in the distal common carotid artery (the arterial segment 1 cm proximal to the carotid bulb), bulb, and proximal internal carotid artery (the arterial segment 1 cm distal to the carotid bifurcation) using dedicated software (QLab 6.0, Philips), and was analyzed by the same investigator, who was blinded to all clinical information. The mean IMT values of 6 arterial segments were measured, the mean and maximum of which were calculated for further analysis. Our study involved a single ultrasonographer and a single reader. The intraclass correlation coefficient (ICC) for the mean of the 12 site-specific maximum IMT values was 0.97[26].

PWA protocol. Participants had PWA in the morning, having fasted overnight, and were asked to avoid tobacco, alcohol, and caffeine 3 h before measurement, as reported[27]. Participants rested in a sitting position in a quiet room for at least 10 min before examination. BP was measured 3 times at the right brachial artery using a validated oscillometric device (Omron HEM-757). PWA was performed using the SphygmoCor device (SCOR2000 v. 7.01, AtCor Medical Pty. Ltd.) with a tonometer probe at the right radial artery. The central aortic arterial pulse wave was transferred from the peripheral arterial pulse wave automatically. Because augmentation index (AIx) in an individual patient varies by heart rate, it is commonly standardized to a heart rate of 75 beats/min.

Brachial-ankle pulse wave velocity (baPWV) was assessed non-invasively in subjects in the supine position by a dedicated tonometry system

(Non-Invasive Vascular Profile Device VP-2000; Omron Healthcare Inc.) as described[28]. The machine measured and recorded results of electrocardiogram, phonocardiogram, and BP of limbs as well as pulse waveforms of limb arteries automatically. The difference in the times of the start of the pulse waves was corrected for distance to obtain the baPWV. All PWA measurements were made by a single skilled operator. Intraobserver reliability ICC was 0.86.

The method of concealed random allocation was used. Simple randomization was conducted by a computer-generated random list.

Outcomes. The primary outcomes were the progression of subclinical atherosclerosis and arterial stiffness markers, as evaluated by IMT, AIx, and PWV over a period of 6 months.

Per-protocol analysis was performed to assess whether there were any differences in the progression of atherosclerosis and vascular stiffness between early and delayed IFX treatment. The MTX ± delayed IFX group (n = 19) consisted of 5 patients who received 1 year of MTX and 14 patients who received escape therapy from Week 24 to Week 46. The MTX + early IFX group (n = 16) consisted of patients who received 1 year of combination therapy (Figure 1). Secondary atherosclerosis outcomes included reduction in progression of IMT, AIx, and PWV over 12 months.

Statistical analysis. Results are expressed as mean ± SD for normally distributed data. Non-normally distributed data are expressed as median (interquartile range). Student's t test or Mann-Whitney U test were used to compare continuous variables between groups. The chi-squared test or Fisher's exact tests were used to compare categorical variables between groups. Data at 6 months were analyzed according to the intention-to-treat (ITT) principle in all individuals with at least 1 additional visit after the baseline. Missing data at the end of the study were accounted for using last observation carried forward. The longitudinal effects of early IFX therapy (Group B) compared to delayed IFX therapy (Group A) on various clinical and laboratory assessments and subclinical atherosclerosis and arterial stiffness markers during the 12-month followup period were examined as the interaction between the therapy group and time using repeated-measure ANOVA. A minimal level of significance of $p < 0.05$ was used. All tests were 2-tailed. All statistical analyses were conducted using SPSS 15.0 for Windows.

Sample size calculation. The sample size is estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS). Based on a previous study in patients with psoriatic arthritis, the rate of change in the mean IMT was –0.0137 mm/year (SD 0.02916, 95% CI –0.0381 to 0.0106) and 0.0129 mm/year (SD 0.02743, 95% CI 0.0001 to 0.0257) in the TNF-α blocker-treated (n = 9) and TNF-α-naive group (n =

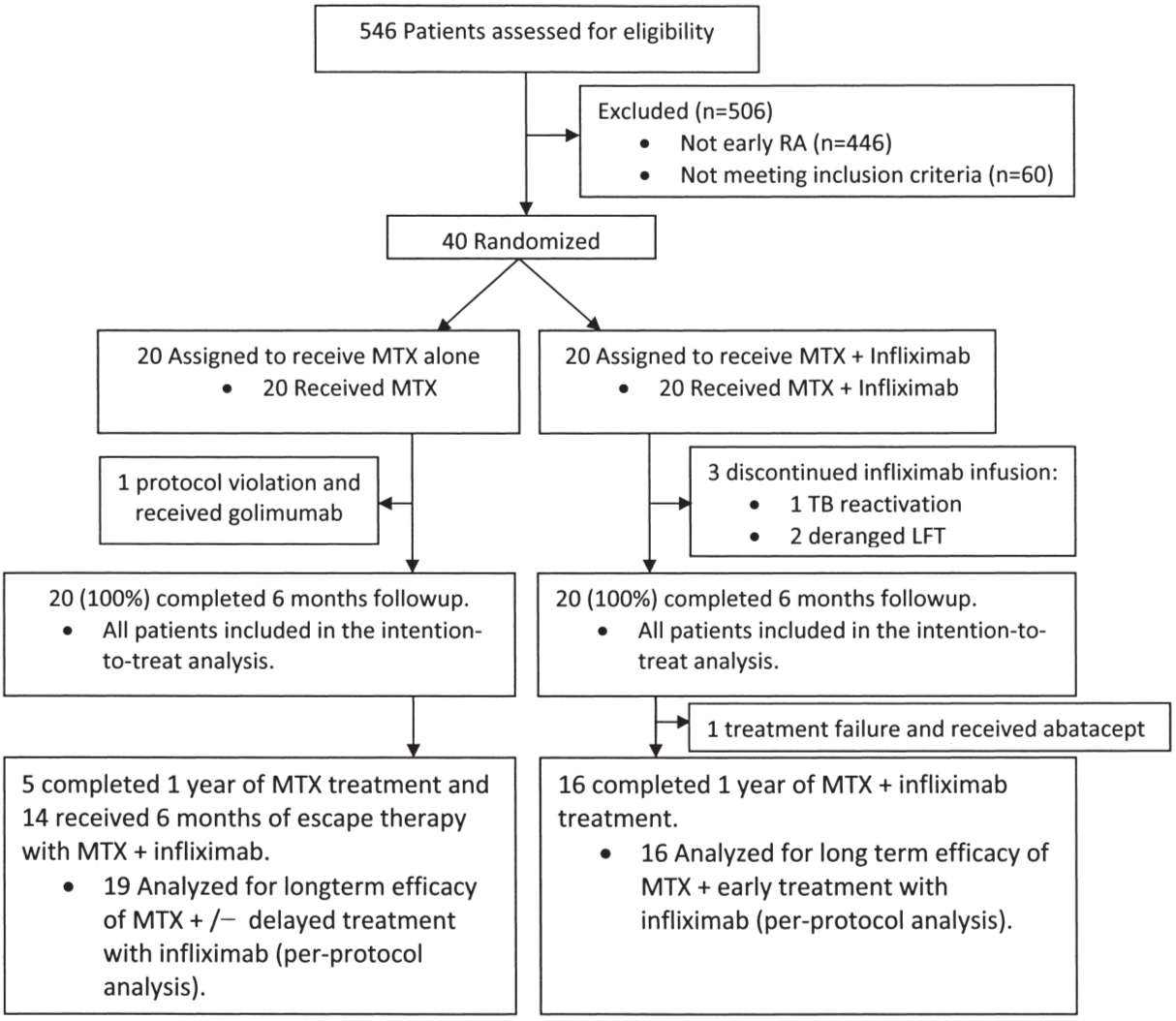

Figure 1. Study participants and progress of the study. TB: tuberculosis; LFT: liver function tests.

20), respectively[29]. Sample size of 18 per arm would achieve 80% power to detect a difference between the groups at a significance level (α) of 0.05 using a 2-sided Student's t test. Allowing a 10% dropoff, a total sample size of 40 would be needed.

RESULTS

Clinical features of patients with early RA. The baseline demographic, clinical and treatment variables, and cardiovascular risk factors and vascular assessments are summarized in Tables 1 and 2. All these variables were similar between the 2 groups except disease activity, which was significantly higher in the MTX + IFX group compared with the MTX-alone group (Table 2).

At 6 months, 1/20 subjects (5%) in the MTX-alone group had received golimumab because of inefficacy, while 3/20 (15%) in the MTX + IFX group required discontinuation of MTX and IFX because of adverse events (for 1, reactivation of latent tuberculosis infection, and for 2, increase in liver enzymes; Figure 1). None of the patients changed dosage or type of antihypertensive or received lipid-lowering medication throughout the study period.

Intention-to-treat analysis. At 6 months, 5/20 (25%) and 9/20 (45%) patients achieved remission in the MTX-alone group and the MTX + IFX group, respectively ($p > 0.05$). The reductions of the disease activity and inflammatory markers were significantly greater in the MTX + IFX group compared with the MTX-alone group (Table 2). The markers were patient's global assessment (PtGA; $p = 0.006$), number of swollen joints (SJC; $p = 0.042$), DAS28 ($p = 0.01$), and CRP ($p = 0.007$).

MTX plus IFX showed superior efficacy to MTX alone regarding the change in PWV after 6 months (0.18 ± 1.59 m/s in the MTX-alone group vs –0.78 ± 1.13 m/s in the MTX + IFX group; $p = 0.044$; Figure 2). No significant changes in IMT and AIx were observed in the 2 groups. Changes in PWV in patients randomized to receive MTX + IFX who did (n = 9, –0.87 ± 1.40 m/s) or did not achieve DAS remission (n = 11, –0.69 ± 0.87 mm/s; $p = 0.746$) were similar. There were no significant between–group differences in the changes in all the CV risk factors, including BP (Table 2). Moreover, the changes in PWV of the 40 patients did not correlate with the change in systolic BP (SBP; $r = –0.042$, $p = 0.807$) or diastolic BP (DBP; $r = 0.103$, $p = 0.550$).

Per-protocol analysis. After 6 months, 1 more patient from the MTX + early IFX group dropped out because of inefficacy (Figure 1). For those who completed the protocol, 11/19 (58%) and 8/16 (50%) patients achieved remission in the MTX ± delayed IFX group and the MTX + early IFX group, respectively, at 12 months. In the repeated-measure ANOVA, the MTX + early IFX group [5.0 (IQR 5.0, 6.0) at baseline, 1.0 (IQR 0, 2.0) at 6 months, and 0 (IQR 0, 2.8) at

Table 1. Baseline demographic and clinical characteristics of the patients with early rheumatoid arthritis. Data are mean ± SD or median (interquartile range) unless otherwise specified.

Characteristic	Methotrexate Alone, n = 20	Methotrexate + Infliximab, n = 20	p
Age, yrs	53 (43, 59)	53 (47, 61)	0.713
Sex M/F, n (%)	5 (25)/15 (75)	1 (5)/19 (95)	0.077
Disease duration, mo	5.8 (2.0, 11.9)	4.2 (3.1, 8.6)	0.468
Current smoker, n (%)	3 (15)	0	0.076
Diabetes mellitus, n (%)	0	1	0.500
Hypertension, n (%)	4 (20)	6 (30)	0.358
Hyperlipidemia, n (%)	0	0	
Disease severity, n (%)			
RF-positive	18 (90)	14 (70)	0.114
ACPA-positive	19 (95)	16 (80)	0.267
Erosion on radiograph	4 (20)	2 (10)	0.376
Extraarticular features, n (%)			
Rheumatoid nodule	3 (15)	1 (5)	0.292
Sicca	2 (10)	2 (10)	1.000
Cardiovascular drugs and DMARD ever, n (%)			
Statins	0	0	
ACEI	0	0	
Beta blockers	2 (10)	2 (10)	0.698
Calcium channel blockers	3 (15)	5 (25)	0.347
NSAID	18 (90)	19 (95)	0.500
Methotrexate	20 (100)	20 (100)	1.000
Leflunomide	0	1 (5)	0.311
Hydroxychloroquine	1 (5)	1 (5)	1.000
Corticosteroid	3 (15)	6 (30)	0.256

RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; DMARD: disease-modifying antirheumatic drug; ACEI: angiotensin-converting enzyme inhibitors; NSAID: nonsteroidal antiinflammatory drugs.

Table 2. Intention-to-treat analysis: changes in disease activity indices, markers of inflammation and cardiovascular risk factors over 6 months. Data are mean ± SD or median (interquartile range).

Measure	Methotrexate Alone, n = 20		Methotrexate + Infliximab, n = 20		p*
	Baseline	Changes After 6 Months	Baseline	Changes After 6 Months	
Disease activity indices and markers of inflammation					
EMS, min	45 (15, 120)	–17.5 (–93.8, 0.0)	45 (16, 113)	–23.5 (–57.5, 2.3)	0.645
Pain, VAS 0–10	6.3 ± 2.4	–2.1 ± 2.6	7.1 ± 2.1	–3.7 ± 2.5	0.062
PtGA, VAS 0–10	5.6 ± 2.6	–0.8 ± 3.2	7.1 ± 2.3	–3.6 ± 2.9	0.006
PhGA, VAS 0–10	7.0 (5.3, 9.0)	–3.0 (–4.9, 0.0)	7.0 (6.0, 8.0)	–4.0 (–5.9, –3.3)	0.091
TJC	9.9 ± 6.3	–4.2 ± 5.0	9.8 ± 3.8	–4.9 ± 5.0	0.685
SJC	5.0 (4.0, 7.0)	–2.0 (–4.0, 0.75)	5.0 (4.6, 8.0)	–4.0 (–5.8, –3.0)	0.042
DAS28	4.6 ± 0.7	–1.0 ± 1.3	5.1 ± 0.7#	–2.0 ± 0.9	0.010
HAQ	1.1 ± 0.7	–0.3 ± 0.6	1.5 ± 0.7	–0.6 ± 0.5	0.078
ESR, mm/h	55 ± 38	13 ± 22	65 ± 30	–22 ± 23	0.217
CRP, mg/l	13.7 (9.8, 21.9)	–6.6 (–14.5, –0.95)	23.6 (7.7, 36.8)	–17.7 (–29.1, –6.3)	0.007
Cardiovascular risk factors					
Glucose, mmol/l	5.1 ± 0.7	0.1 ± 0.3	4.9 ± 0.6	–0.0 ± 0.3	0.119
TG, mmol/l	1.0 ± 0.5	0.1 ± 0.3	1.1 ± 0.7	0.1 ± 0.5	0.881
TC, mmol/l	4.3 ± 1.3	0.3 ± 0.8	4.5 ± 0.9	0.3 ± 0.6	0.982
HDL-C, mmol/l	1.4 ± 0.3	0.1 ± 0.2	1.4 ± 0.4	0.1 ± 0.3	1.000
LDL-C, mmol/l	2.5 ± 1.1	0.1 ± 0.6	2.6 ± 0.8	0.3 ± 0.4	0.119
TC/HDL-C	3.3 ± 0.8	0.1 ± 0.6	3.4 ± 0.8	0.1 ± 0.7	0.565
SBP, mm Hg	130 ± 24	–3 ± 15	129 ± 16	–4.2 ± 13.4	0.786
DBP, mm Hg	80 ± 13	–4.4 ± 10.0	79 ± 10	–1.5 ± 11.1	0.380
BMI, kg/m^2	22.3 ± 3.1	0.2 ± 0.8	22.0 ± 3.5	0.1 ± 0.8	0.664

* Comparison between the changes from baseline between the 2 groups using Student t tests or Mann-Whitney U tests. EMS: duration of early morning stiffness; VAS: visual analog scale; PtGA: patient's global assessment; PhGA: physician's global assessment; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TG: total triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; TJC: tender joint count; SJC: swollen joint count.

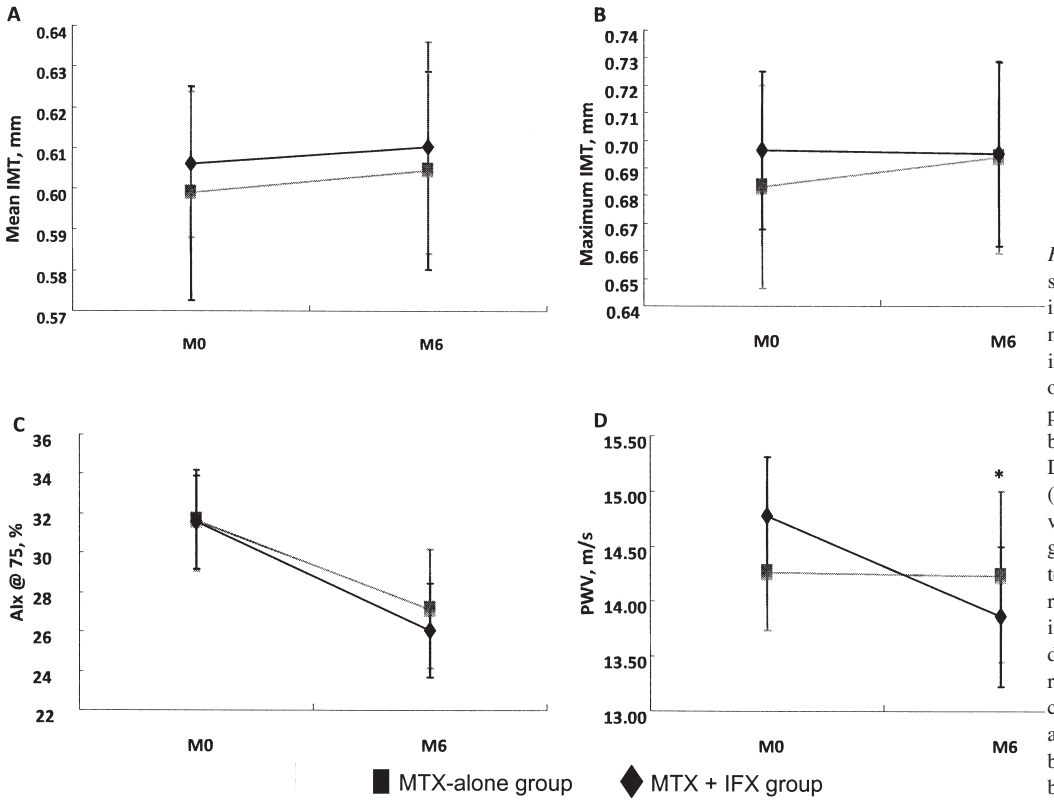

Figure 2. Intention-to-treat analyses: changes in (A) mean intima-media thickness (IMT); (B) maximum IMT; (C) augmentation index standardized to a heart rate of 75 bpm (AIx@75); and (D) pulse wave velocity (PWV) at baseline (M0) and month 6 (M6). Data are presented as the mean (standard error of mean) for each visit. Methotrexate (MTX)-alone group (gray line, rectangle) consisted of 20 patients randomized to receive 1 year of MTX. MTX + infliximab (IFX) group (black line, diamond) consisted of 20 patients randomized to receive 1 year of combination therapy with MTX and IFX. *$p < 0.05$ comparison between the changes from baseline between the 2 groups.

12 months] had a significantly better improvement in the SJC over time than the MTX ± delayed IFX group [5.0 (IQR 4.0, 7.0) at baseline, 3.0 (IQR 1.0, 4.0) at 6 months, and 0 (IQR 0, 2.0) at 12 months; p = 0.031]. Apart from that, there were no significant differences in the change in other disease activity and inflammatory markers between the 2 groups (data not shown).

At 12 months, there were no significant differences between the 2 groups in the changes in atherosclerosis measures (Table 3), although there may be a trend favoring early combination treatment with regard to the reduction in PWV (p = 0.060). There was a nonsignificant increase in the PWV over 12 months in the MTX ± delayed IFX group, mainly due to the increase in PWV in the 5 patients who received 1 year of MTX (baseline: 13.04 ± 2.83 m/s; 12 months: 14.29 ± 4.26 m/s), while PWV remained stable for those 14 patients who received MTX + delayed IFX (baseline: 14.43 ± 2.17 m/s; 12 months: 14.43 ± 3.34 m/s). Further, there were no significant between-group differences in the changes over time in the CV risk factors (data not shown). Similar to the intention-to-treat analysis, the changes in PWV of the 35 patients did not correlate with the change in SBP (r = –0.271, p = 0.127) or DBP (r = 0.246, p = 0.179).

DISCUSSION

To our knowledge, this is the first RCT comparing the vascular effect of MTX plus IFX with MTX alone in patients with early RA. We confirmed that 6 months' treatment of MTX plus IFX was superior to MTX alone in improving arterial stiffness in early RA patients with active disease, as evidenced by a significantly greater reduction in PWV, independent of the CV risk factors. This change was associated with a significantly greater extent of improvement in the clinical (PtGA, SJC, DAS28) and laboratory indicators of inflammation (CRP), suggesting that effective control of inflammation by IFX may prevent progression of atherosclerosis by improving arterial function. The changes in PWV were similar in patients randomized to receive MTX plus IFX regardless of whether DAS remission was achieved. Nonetheless, the results are difficult to interpret because of the small sample size. Our results were consistent with a recent RCT comparing the effect of various biologics monotherapies using PWV adjusted for BP (cardio-ankle vascular index)[21], and other observational or nonrandomized controlled studies[30,31]. Inflammation leads to the activation of endothelial cells, which, through an increase in the expression of leukocyte adhesion molecules, promotes a proatherosclerotic environment[32]. Endothelial dysfunction may affect arterial stiffness through nitric oxide (NO), which is important in arterial stiffness regulation[33]. Inflammatory cytokines may also act through upregulation of angiotensin type 1 receptors to cause vasoconstriction and hypertension[34]. Further, an injury to the endothelium can proceed to intimal thickening with a decrease in vascular wall contractile elements, as smooth muscle cells migrate to the intima, multiply, and lay down the extracellular matrix. The resultant arterial stiffening is characterized by increased vascular collagen formation, calcification, and breakdown of elastin[35]. Our study also provides preliminary evidence that effective control of inflammation by early IFX treatment may be associated with greater improvement of the PWV at 1 year compared to those whose treatments were delayed by 6 months. This improvement occurs most likely because sustained reduction in PWV was possible in patients who continued on longterm IFX, accompanied by a sustained improvement in the clinical markers of inflammation (as reflected by a significantly better improvement in the SJC in the early treatment group compared to the delayed treatment group), independent of the CV risk factors. Apart from suppression of inflammation, other mecha-

Table 3. Per-protocol analysis: changes in vascular measures over 12 months. Data expressed in mean ± SD. Methotrexate (MTX) ± delayed infliximab (IFX) group consisted of 5 patients who received 1 year of MTX and 14 patients who received escape therapy with MTX and IFX from Week 24 to Week 46. MTX + early IFX group consisted of 16 patients who received 1 year of combination therapy with MTX and IFX.

Measure	Baseline	6 Months	12 Months	Changes After 12 Months	p
Mean IMT, mm					
MTX ± delayed IFX, n = 19	0.62 ± 0.10	0.61 ± 0.10	0.60 ± 0.12	–0.00 ± 0.09	0.925
MTX + early IFX, n = 16	0.62 ± 0.08	0.63 ± 0.10	0.63 ± 0.12	0.00 ± 0.11	
Max IMT, mm					
MTX ± delayed IFX, n = 19	0.70 ± 0.16	0.70 ± 0.15	0.73 ± 0.15	0.04 ± 0.11	0.948
MTX + early IFX, n = 16	0.72 ± 0.13	0.72 ± 0.14	0.77 ± 0.16	0.06 ± 0.11	
AIx @ 75, %					
MTX ± delayed IFX, n = 19	31.6 ± 11.5	27.2 ± 12.7	22.0 ± 11.1	–8.1 ± 12.7	0.438
MTX + early IFX, n = 16	34.0 ± 10.1	28.0 ± 9.0	30.0 ± 6.1	–4.2 ± 11.6	
PWV, m/s					
MTX ± delayed IFX, n = 19	14.19 ± 2.39	14.23 ± 3.28	14.39 ± 3.49	0.24 ± 2.01	0.060
MTX + early IFX, n = 16	14.51 ± 2.31	13.79 ± 2.24	13.40 ± 2.49	–1.06 ± 1.27	

P values for between-group comparisons of changes over 1 year. IMT: intima-media thickness; PWV: pulse wave velocity; AIx @ 75: augmentation index standardized to a heart rate of 75 bpm.

nisms whereby IFX may improve arterial stiffness may include preventing endothelial dysfunction through a decrease in the production of cytotoxic concentrations of NO[36], or by preventing injury to the endothelium and thereby inhibiting perivascular leukocyte infiltration and subsequent vascular smooth muscle cell proliferation[37]. Further studies are required to assess whether IFX reduces arterial stiffening by means of downregulating angiotensin type 1 receptors to cause vasodilation, and to assess whether IFX reduces arterial stiffening by preventing vascular collagen formation, calcification, and breakdown of elastin.

Arterial stiffness is increasingly recognized as a surrogate endpoint for CV disease and is associated with the presence of CV risk factors and atherosclerotic diseases[35]. Arterial stiffness can be measured with noninvasive, reproducible, and relatively inexpensive techniques suitable for large-scale studies. Carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard for assessing aortic stiffness[38] and predicts future CV events and all-cause mortality in a strong and independent manner[38a]. Brachial-ankle PWV, calculated as the ratio of the distance between the brachial and the tibial artery divided by the transit time between these 2 arteries, has been proposed as an additional arterial biomarker of CV risk. Use of this index has been popularized primarily in East Asian countries over the past 13 years and has been shown in cross-sectional comparisons to be associated with CV risk factors and function, as well as CV disease, similarly to cfPWV[40]. The observed difference of 1 m/s in the group that received 1 year of MTX + IFX was remarkable, because a metaanalysis[39] showed that an increase in baPWV by 1 m/s corresponded with an increase of 12%, 13%, and 6% in total CV events, CV mortality, and all-cause mortality, respectively.

We did not find any differences in the changes in AIx after 6 months of MTX with or without IFX therapy in the ITT analysis, or between early and delayed IFX treatment at 12 months in the per-protocol analysis. Apart from a cohort study that reported that treatment with etanercept reduced AIx[41], the majority of previous studies did not report any change in AIx after TNF-α antagonists[20,42,43,44]. AIx is a composite measure dependent on the magnitude and site of pulse wave reflection in addition to the speed of the reflected wave. Central arterial stiffness (PWV) and peripheral reflectance are important determinants of the AIx. Therefore, not only macrovascular functions, but also microvascular functions affect the AIx. Results from our study as well as others may suggest that PWV may be a more sensitive marker reflecting improvement of predominantly macrovascular functions in patients receiving TNF blockers. Further, normalization of peripheral vasculature tonus and an increase in wave reflection may also occur after initiation of anti-TNF-α therapy.

Similarly to AIx, no differences were noticed regarding the changes in IMT after 6 months of MTX with or without IFX therapy in the ITT analysis, or early compared to delayed IFX therapy in the per-protocol analysis. Our results concurred with previous reports that the IMT did not change significantly after 12 to 18 months of treatment with a TNF-α blocker[20,45]. Progression of IMT has been described in 8 patients with longstanding RA who had maintained a high disease activity despite at least 2-year treatment with IFX[46]. In contrast, 2 other reports demonstrated IMT reduction in patients with RA[47,48]. Evaluation of the regression of subclinical atherosclerosis by carotid arterial ultrasound examination following treatment of risk factors takes time (i.e., more than 1 year is required in most cases to confirm such regression). Longer-term studies may be required to clarify this issue. Results from our study also suggest that these commonly used "surrogate" markers of atherosclerotic vascular disease are not necessarily interchangeable and that PWV may be more responsive to change over a short period of time than IMT.

The strength of our study was the randomized, controlled design and the inclusion of patients with short disease duration in whom changes in the vessel wall may reflect current (but reversible) inflammation rather than more permanent structural vessel changes. In Hong Kong, the cost of TNF inhibitors is not reimbursed by the government, but patients who fulfill the Hong Kong guidelines for the use of TNF blockers[49] can apply for financial assistance, provided they meet certain income limits. As a result, most patients in Hong Kong treated with anti-TNF need to cover the medication costs themselves. Our study was considered ethical by the local ethics committee and was welcomed by patients because they all received free medications.

Limitations of the trial included, first, the use of surrogate endpoints instead of actual CV events. There is virtually no data to suggest that such vascular assessments are good predictors of future CV events specifically in patients with RA. There is a single study suggesting this for IMT (n = 47)[50], and another study by the del Rincon group suggesting that plaque is predictive[51]. Second, the sample size was small because this was only a pilot study to obtain preliminary evidence. Third, because we have included Chinese patients with short disease duration who are stable with moderate to severe disease activity, these results may not be generalizable to patients with RA who are from other ethnic backgrounds, have long disease duration, or have mild disease activity. Fourth, the lack of vascular outcome measures before 24 weeks means that we may have missed any earlier changes that may revert to baseline within the timeframe of assessment. Fifth, whether longer treatment duration may be required for the process of inflammation suppression on atherosclerotic disease progression in patients with RA remained uncertain. Lastly, the fluctuating disease activity during the course of our study may also contribute to the changes in the vascular assessment measures.

These results demonstrate that 6 months of MTX and

IFX therapy was superior to MTX alone in improving arterial stiffness in terms of PWV reduction in patients with early RA. Further, early treatment with IFX may be beneficial, because sustained improvement in the PWV may be achieved in patients who continued receiving IFX in association with improvement in clinical indices of inflammation, but independent of changes in metabolic and CV profiles, probably by lowering inflammatory mediators of atherosclerosis.

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