The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis—a randomized, placebo-controlled pilot trial

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Abstract

Objective. Our aim was to ascertain the efficacy of golimumab compared with placebo in the prevention of atherosclerosis and arterial stiffness in AS.

Methods. A randomized, double-blind, placebo-controlled pilot study was performed in which AS patients were treated with golimumab (n=20) and placebo (n=21) for 12 months. Patients from the placebo group who failed to achieve a 20% response to Assessment of SpondyloArthritis international Society criteria (ASAS20) at 6 months received open-label golimumab. Intima–media thickness (IMT), pulse wave velocity (PWV) and augmentation index (Alx) were measured at baseline, 6 and 12 months.

Results. At 6 months, 11/20 (55%) and 3/21 (14%) patients from the golimumab and placebo groups achieved an ASAS20 response, respectively (P=0.006). There was no significant difference in the change of the vascular parameters between the two groups. In the placebo group, significantly greater progression of the mean IMT [from 0.51 mm (s.d. 0.07) at baseline to 0.53 mm (s.d. 0.08) at 6 months, P=0.044] and PWV (from 12.2 m/s (s.d. 1.6) at baseline to 12.6 m/s (s.d. 1.3), P=0.028) were observed. There was a trend towards progression of the mean IMT in the golimumab group (P=0.099) but the maximum IMT, PWV and Alx remained unchanged. At 12 months the changes in vascular parameters were similar between the early and delayed (or no) golimumab groups.

Conclusion. Uncontrolled inflammation may result in a significant progression in IMT and PWV in patients with AS. Arterial dysfunction may be prevented by golimumab over a period of 6 months, probably because of effective suppression of inflammation.

Trial registration: clinicaltrials.gov (NCT01212653)

Key words: golimumab, intima–media thickness, pulse wave velocity, ankylosing spondylitis, randomized placebo-controlled trial.

Introduction

Patients with AS are known to have an overall mortality of about 1.6–1.9 times that of the general population, and excess mortality from cardiovascular diseases (CVDs) has been estimated at 20–40% [1–3]. Whether there is an increase in myocardial infarction [4–7] in AS patients compared with controls remains controversial, although the prevalence of ischaemic heart disease (IHD) [7–10] appears to be increased.
Methods

Trial design

This was a prospective, randomized, double-blind, placebo-controlled, single-centre pilot study.

Study subjects

Inclusion criteria

Forty-one consecutive patients with AS attending the outpatient clinic of the Prince of Wales Hospital and who fulfilled the Assessment of SpondyloArthritis International Society (ASAS) guidelines for anti-TNF-α treatment were studied [27]. All patients who fulfilled the modified New York criteria of AS [28] for more than 3 months with a BASDAI [29] score ≥4 (0–10-point scale), a spinal pain assessment score ≥4 on a visual analogue scale (VAS; 0–10-cm scale) and an inadequate response to at least two NSAIDs during a 3-month period, failure of IA steroids (if indicated) and failure of SSZ in patients with predominantly peripheral arthritis were eligible for participation in the study. Patients could continue stable MTX, SSZ, corticosteroids (prednisolone ≤10 mg/day) and NSAID treatment. Patients treated with antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors and statins, were allowed but had to be maintained on the same dosage throughout the study period.

Exclusion criteria

Patients were excluded from the study if they had any of the following: complete ankylosis of the spine, any other inflammatory rheumatic disease, contraindications to treatment with golimumab, or were females of childbearing potential who were unwilling to use adequate contraception and pregnant or breastfeeding women. Patients were also ineligible if they had a history of overt CVD.

Study protocol

Patients were examined clinically at week 0 and every 3 months thereafter until the end of the study, which included clinical examinations and laboratory tests. Carotid US, PWV and pulse wave analysis (PWA) were performed at baseline, 6 and 12 months. The Clinical Research Ethics Committee of the Chinese University of Hong Kong approved the study and informed consent was obtained from all patients.

Intervention

Forty-one AS patients were randomly assigned to receive either s.c. golimumab 50 mg/month or matching placebo for 12 months using a 1:1 randomization procedure.

Clinical interview

All patients were interviewed and examined with the use of standardized data collection instruments. Disease activity was evaluated using the BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS). Physical function was evaluated using the BASFI. Range of motion was assessed using the BASMI (3-point scale). Anthropomorphic measurements included height and weight, two consecutive blood pressure (BP) readings in a sitting position and heart rate.

Blinding

The doctors responsible for clinical assessment, the patients and the nurse who administered the study medication were blinded. An unblinded nurse was responsible for preparing the study medication. At 6 months, patients who failed to achieve a 20% response in ASAS criteria (ASAS20) were unblinded. Patients receiving placebo were permitted to receive open-label golimumab treatment. All other patients continued to receive their assigned treatment.

Laboratory tests

Complete blood count, liver and renal function tests, ESR and CRP, fasting blood glucose, lipid profile (total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs)) were checked every 3 months.

Carotid IMT and plaque

Carotid IMT was measured using a high-resolution B-mode US machine (iE33, Philips, Andover, MA, USA). Briefly, duplex carotid US was performed by an experienced cardiologist (Q.S.) using an 11-MHz linear vascular probe. The IMT was measured offline in the distal carotid artery wall.
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, Andover, MA, USA) and was analysed by the same investigator who was blinded to all clinical information. The mean IMT values of six 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 [30].

Pulse wave analysis

Participants received PWA examination in the morning, having fasted overnight, and were asked to avoid tobacco, alcohol and caffeine within 3 h before measurement, as previously reported [30]. Participants rested in a sitting position in a quiet room for at least 10 min before examination. BP was measured three times at the right brachial artery using a validated oscillometric device (Omron HEM-757, Omron Healthcare, Vernon Hills, IL, USA). PWA was performed using the SphygmoCor device (SCOR2000 version 7.01, AtCor Medical, West Ryde, NSW, Australia) with a tonometer probe at the right radial artery. The central aortic arterial pulse wave was transferred from the peripheral arterial pulse wave automatically. Since the aortic augmentation index (AIX) in an individual patient varies by heart rate, it is commonly standardized to a heart rate of 75 bpm (AIX@75).

Brachial-ankle PWV (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) as described previously [30]. The machine automatically measures and records results of the electrocardiogram, phonocardiogram and BP of the limbs as well as pulse waveforms of the limb arteries. Differences in the time of the start of the pulse waves were corrected for distance to obtain the baPWV. All PWA measurements were made by a single skilled operator. Intraobserver reliability ICC was 0.86.

Randomization

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

Outcomes

(i) Intention to treat (ITT). 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.

(ii) Per-protocol analysis was performed to assess whether there were any differences in the progression of atherosclerosis and vascular stiffness between early and delayed golimumab treatment.

The placebo and delayed golimumab groups ($n=20$) consisted of 3 patients who received 1 year of placebo and 17 patients who received escape therapy from 6 to 12 months. The early golimumab group ($n=19$) consisted of patients who received 1 year of golimumab therapy (Fig. 1). Secondary atherosclerosis outcomes included a reduction in progression of IMT, AIX and PWV over a period of 12 months.

Statistical analysis

Results are expressed as mean (s.d.) for normally distributed data and as median [interquartile range (IQR)] for non-normally distributed data. Student’s $t$-test or Mann–Whitney $U$ test was 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 analysed according to the ITT principle in all individuals with at least one additional visit after the baseline. Missing data at the end of the study were accounted for using the last observation carried forward. At 6 months, patients who failed to achieve an ASAS20 response, discontinued treatment because of an adverse event or who were missing all ASAS components were considered to be non-responders. The longitudinal effects of early golimumab therapy compared with placebo or delayed golimumab therapy on various clinical and laboratory assessments and subclinical atherosclerosis and arterial stiffness markers during the 12-month follow-up period were examined as the interaction between the therapy group and time using repeated measures analysis of variance (ANOVA). A minimal level of significance of $P < 0.05$ was used. All tests were two-tailed. All statistical analyses were conducted using SPSS 15.0 for Windows (IBM, Armonk, NY, USA).

Sample size calculation

The sample size is estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Kaysville, UT, USA). Based on a previous study in patients with PsA, the rate of change in the mean IMT was $-0.0137 \text{ mm/year (s.d.)} \pm 0.02916$, 95% CI $-0.0381$, $0.0106$ and $0.0129 \text{ mm/year (s.d.)} \pm 0.02743$, 95% CI $0.0001$, $0.0257$ in the TNF-$\alpha$ blocker–treated ($n=9$) and TNF-$\alpha$–naive ($n=20$) groups, respectively [31]. A sample size of 18 per arm would achieve 80% power to detect a difference between the groups at a significance level ($\alpha$) of 0.05 using a two-sided Student’s $t$-test. Allowing a 10% of drop off, a total sample size of 40 would be needed.

Results

Clinical features of AS patients

The baseline demographic, clinical, treatment variables and CV risk factors and vascular assessments are
summarized in Tables 1–4. All these variables were similar between the two groups except that the BASMI is significantly higher in the golimumab group (Table 2).

At 6 months, 1 of 21 subjects (5%) in the placebo group withdrew from the study because of a severe adverse event (intracerebral haemorrhage), while 1 of 20 (5%) subjects in the golimumab group was lost to follow-up. None of the patients changed dosage or type of antihypertensive or received new lipid-lowering medication throughout the study period.
Effects of golimumab on subclinical atherosclerosis and arterial stiffness in AS

**Table 2** ITT analysis: changes in disease activity indices and markers of inflammation over 6 months

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 21)</th>
<th>Golimumab (n = 20)</th>
<th>P-value*</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Changes after 6 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>ESR, median (IQR), mm/h</td>
<td>20 (14.5–35.0)</td>
<td>–5 (–12.5–5)</td>
<td>29.0 (22.5–47.2)</td>
</tr>
<tr>
<td>CRP, mean (s.d.), mg/l</td>
<td>19.9 (14.0)</td>
<td>–4.83 (18.6)</td>
<td>23.9 (18.6)</td>
</tr>
<tr>
<td>Total back pain, median (IQR), VAS 0–10</td>
<td>7 (6–8)</td>
<td>0.0 (–1.5–1)</td>
<td>7 (6.25–8)</td>
</tr>
<tr>
<td>PGA, mean (s.d.), VAS 0–10</td>
<td>6.38 (1.75)</td>
<td>–0.26 (2.37)</td>
<td>6.15 (1.98)</td>
</tr>
<tr>
<td>Inflammation, mean (s.d.), VAS 0–10</td>
<td>5.5 (5–7)</td>
<td>0.0 (–1.25–0.5)</td>
<td>6.0 (5.5–7.0)</td>
</tr>
<tr>
<td>Morning stiffness, median (IQR), min</td>
<td>60 (60–90)</td>
<td>0 (–30–0)</td>
<td>60 (30–90)</td>
</tr>
<tr>
<td>BASDAI, mean (s.d.), VAS</td>
<td>6.14 (1.52)</td>
<td>–0.66 (1.24)</td>
<td>6.15 (1.02)</td>
</tr>
<tr>
<td>BASFI, mean (s.d.), VAS 0–10</td>
<td>41.0 (23.2)</td>
<td>1.73 (7.20)</td>
<td>46.1 (18.5)</td>
</tr>
<tr>
<td>ASAS (CRP), mean (s.d.)</td>
<td>3.0 (2.0–5.5)b</td>
<td>0.0 (–1.0–0.0)</td>
<td>5.0 (4.0–7.0)b</td>
</tr>
<tr>
<td>ASAS (ESR), median (IQR)</td>
<td>3.53 (3.13–4.2)</td>
<td>–0.35 (–0.86–0.09)</td>
<td>3.64 (3.37–4.09)</td>
</tr>
</tbody>
</table>

ITT: intention to treat; IQR: interquartile range; VAS: visual analogue scale; PtGA: patient’s global assessment; PGA: physician’s global assessment. *Comparison between the changes from baseline between the two groups using Student’s t-test or Mann-Whitney U test. **P < 0.05 at baseline comparing the placebo and golimumab groups.

**Table 3** Changes in vascular parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>P-valuea</th>
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<tbody>
<tr>
<td></td>
<td>Mean IMT, mm</td>
<td></td>
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<tr>
<td>ITT analysis</td>
<td>Placebo (n = 21)</td>
<td>0.51 (0.07)</td>
<td>0.53 (0.08)</td>
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<td></td>
<td>Golimumab (n = 19)</td>
<td>0.52 (0.07)</td>
<td>0.54 (0.09)</td>
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<tr>
<td></td>
<td>Maximum IMT, mm</td>
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<td></td>
<td>Placebo (n = 21)</td>
<td>0.54 (0.08)</td>
<td>0.56 (0.10)</td>
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<td></td>
<td>Golimumab (n = 19)</td>
<td>0.56 (0.09)</td>
<td>0.56 (0.10)</td>
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<td></td>
<td>baPWV, m/s</td>
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<td></td>
<td>Placebo (n = 21)</td>
<td>12.19 (1.56)</td>
<td>12.63 (1.32)</td>
</tr>
<tr>
<td></td>
<td>Golimumab (n = 19)</td>
<td>12.41 (1.46)</td>
<td>12.35 (1.57)</td>
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<td></td>
<td>Aortic Aix@75%, %</td>
<td></td>
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<tr>
<td></td>
<td>Placebo (n = 21)</td>
<td>12.35 (10.3)</td>
<td>11.60 (10.9)</td>
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<tr>
<td></td>
<td>Golimumab (n = 19)</td>
<td>11.4 (11.8)</td>
<td>13.1 (10.9)</td>
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<td></td>
<td>Per-protocol analysis</td>
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<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>12 months</td>
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<tr>
<td></td>
<td>Mean IMT, mm</td>
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<td></td>
<td>PD-Go group (n = 20)</td>
<td>0.51 (0.08)</td>
<td>0.53 (0.09)</td>
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<td></td>
<td>E-Go group (n = 19)</td>
<td>0.54 (0.08)</td>
<td>0.55 (0.10)</td>
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<td></td>
<td>Maximum IMT, mm</td>
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<td></td>
<td>PD-Go group (n = 20)</td>
<td>0.54 (0.08)</td>
<td>0.57 (0.10)</td>
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<td></td>
<td>E-Go group (n = 19)</td>
<td>0.57 (0.09)</td>
<td>0.57 (0.10)</td>
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<td></td>
<td>baPWV, m/s</td>
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<td></td>
<td>PD-Go group (n = 20)</td>
<td>12.36 (1.39)</td>
<td>12.70 (1.34)</td>
</tr>
<tr>
<td></td>
<td>E-Go group (n = 19)</td>
<td>12.41 (1.60)</td>
<td>12.48 (1.57)</td>
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<tr>
<td></td>
<td>Aortic Aix@75%, %</td>
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<td></td>
<td>PD-Go group (n = 20)</td>
<td>13.18 (10.52)</td>
<td>12.59 (11.47)</td>
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<tr>
<td></td>
<td>E-Go group (n = 19)</td>
<td>11.82 (12.28)</td>
<td>13.24 (11.32)</td>
</tr>
</tbody>
</table>

Data expressed as mean (s.d.). ITT: intention to treat; IMT: intima-media thickness; baPWV: brachial-ankle pulse wave velocity; Aix@75: augmentation index standardized to a heart rate of 75 bpm; PD-Go group: placebo or delayed golimumab group, which included three patients who received placebo for 12 months and 17 patients who received escape therapy from 6 to 12 months; E-Go group: early golimumab group consisted of 19 patients who received golimumab for 12 months. *Within-group comparison between baseline and 6 months using paired t-tests. **The longitudinal effects of early golimumab therapy compared with placebo or delayed golimumab therapy on subclinical atherosclerosis and arterial stiffness markers during the 12-month follow-up period were examined as the interaction between the therapy group and time using repeated measures ANOVA.
Data are expressed as mean (S.D.) unless stated otherwise. ITT: intention to treat; CV: cardiovascular; TG: total triglycerides; using Student’s t-test. ITT: intention to treat; CV: cardiovascular; TG: total triglycerides; using Student’s t-test. DBP: diastolic blood pressure. Comparison between the changes from baseline between the two groups. IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; AIx: augmentation index. There were no significant differences regarding the change in vascular parameters between the two groups (Table 3). There were no significant differences between the two groups with respect to changes in atherosclerosis measures (Table 3). Apart from a significantly greater increase in HDL levels over time in the early golimumab group compared with the placebo group (Fig. 2), there were no significant differences in the change in other disease activity markers observed between the two groups (data not shown). Changes in atherosclerosis and CV risk factors

There were no significant differences in the changes from baseline between the two groups (Table 4). Using Student’s t-test or Mann-Whitney U test.

### Changes in disease activity and inflammatory markers

At 6 months, 3 of 21 (14%) and 11 of 20 (55%) patients from the placebo and golimumab groups, respectively, achieved an ASAS20 response (P = 0.006) (Fig. 1). The reduction in disease activity and inflammatory markers, including total back pain (P = 0.001), physician’s global assessment (PGA) (P = 0.009), BASDAI (P = 0.015), BASMI (P = 0.018), ASDAS (P < 0.001), ESR (P < 0.001) and CRP (P = 0.034), were significantly greater in the golimumab group compared with the placebo group (Table 2).

### Changes in atherosclerosis and CV risk factors

There were no significant differences regarding the change in vascular parameters between the two groups (Table 3). Nonetheless, within-group comparison showed that in the placebo group significantly greater progression of the mean IMT [from 0.51 mm (s.d. 0.07) at baseline to 0.53 mm (s.d. 0.08) at 6 months, P = 0.044] and PWV [from 12.2 m/s (s.d. 1.6) at baseline to 12.6 m/s (s.d. 1.3), P = 0.028] were observed. While there was a trend suggesting a progression in the maximum IMT [from 0.54 mm (s.d. 0.08) at baseline to 0.56 mm (s.d. 0.10) at 6 months, P = 0.085], AIx remained unchanged. There was a trend suggesting that the mean IMT may also progress in the golimumab group [from 0.52 mm (s.d. 0.07) at baseline to 0.54 mm (s.d. 0.09) at 6 months, P = 0.099], but the maximum IMT, PWV and AIx remained unchanged. Significantly greater increases in the TC, HDL-C and TG levels were observed in the golimumab group. Nevertheless, no significant differences in the changes of the atherogenic index (AI = TC/HDL-C) or other CV risk factors were observed between the two groups, including BP (Table 4).

### Discussion

In this first randomized controlled trial (RCT) comparing the vascular effect of placebo with golimumab in patients with AS, we found that 6 months of treatment with golimumab was effective in preventing the progression of atherosclerosis measures (Table 3). Apart from a significantly greater increase in HDL levels over time in the early golimumab group (P = 0.007; Fig. 2), there were no significant between-group differences in the changes over time in the CV risk factors (data not shown).
improvement in the clinical (total back pain, PGA, BASDAI, BASMI and ASDAS) and laboratory indicators of inflammation (ESR and CRP) in the golimumab group, suggesting that effective control of inflammation may prevent progression of arterial dysfunction.

Different from PWV, the effect of golimumab therapy on the changes in IMT in AS remains controversial. In this study we reported a significant progression of the mean IMT and a trend towards progression of the maximum IMT in the placebo group after 6 months, while a trend towards progression of the mean IMT was also observed in the golimumab group, although the maximum IMT remained unchanged. No differences were noticed regarding the changes in IMT between early compared with placebo or delayed golimumab therapy in the per-protocol analysis. Data with regard to the effects of anti-TNF on the change in IMT in AS patients were also conflicting. A recent longitudinal follow-up study reported that IMT did not change significantly after 5 years of treatment with TNF-α blockers in AS [32]. Similarly, in patients with RA, two RCTs [30, 33] and three other observational studies also did not demonstrate any change in IMT after 6–18 months of treatment with a TNF-α blocker [34–36]. On the other hand, five other reports demonstrated a reduction in IMT in patients with inflammatory arthritis (RA, PsA and AS) [24, 31, 37–39]. These conflicting results may be explained by the different anti-TNF-α drugs used and the inflammatory diseases studied. More importantly, a significant progression of mean IMT was observed in the control group of AS patients with active disease over a period of 6 months. Progression of IMT has been described in AS patients who discontinued anti-TNF-α treatment [39], PsA patients with mild to moderate disease activity not treated with anti-TNF-α [31] and even in eight RA patients who had maintained high disease activity despite at least 2 years of treatment with infliximab [40], suggesting that uncontrolled inflammation in arthritis patients may accelerate the progression of subclinical atherosclerosis. Moreover, evaluation of the regression of subclinical atherosclerosis by carotid arterial US examination following the treatment of risk factors takes time (i.e. >1 year is required in most cases to confirm such regression). Future longer-term studies may be required to clarify this issue.

Similar to other observational studies [25, 26], arterial stiffness markers including AIx and PWV remained unchanged after 6 and 12 months of anti-TNF-α therapy in our patients with AS. Unfortunately, no control groups were included in the previous trials for comparison. Resembling the change in mean IMT, a significant progression of PWV in controls was observed after 6 months. In contrast, data from a non-randomized case–control study in patients with inflammatory arthritis (RA, PsA and AS) showed that long-term anti-TNF-α
therapy may result in a significant improvement in PWV compared with the non-treated group [24]. This could be explained by the inclusion of RA patients, as improvement in PWV was often reported in these patients treated with anti-TNF-α. A recent RCT from our group [30] as well as others [33] confirmed the efficacy of anti-TNF-α therapy in improving PWV in RA patients, similar to other observational or non-randomized controlled studies [24, 41].

Different from PWV, no change in the AIx was observed in the placebo group after 6 months, suggesting that these commonly used surrogate markers of atherosclerotic vascular disease are not necessarily interchangeable and PWV may be more responsive to change over a short period of time than AIx. 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 suggest that PWV may be a more sensitive marker reflecting changes in predominantly macrovascular functions in rheumatic disease patients with chronic inflammation.

Arterial stiffness is increasingly recognized as a surrogate endpoint for CVD and is associated with the presence of CV risk factors and atherosclerotic diseases. Carotid-femoral PWV (cfPWV) is considered the gold standard for assessing aortic stiffness [42] and predicts future CV events and all-cause mortality in a strong and independent manner [43]. The baPWV, calculated as the ratio of the distance between the brachial and tibial arteries divided by the transit time between these two arteries, has been proposed as an additional arterial biomarker of CV risk. The baPWV has been shown in cross-sectional comparisons to be associated with CV risk factors and function, as well as CVD, similar to cfPWV [44]. Inflammation leads to the activation of endothelial cells, and endothelial dysfunction may impact on arterial stiffness through nitric oxide (NO), which is important in arterial stiffness regulation [45]. TNF-α inhibitors improved endothelial function [46] and microcirculation in patients with AS [47], possibly through a decrease in the production of cytotoxic concentrations of NO [48]. A recent study also reported that the serum level of angiotensin-2, a marker of endothelial cell activation, was reduced following the administration of anti-TNF-α drugs in AS patients [49]. Another biological change that may slow the progression of atherosclerosis in AS is improvement in insulin resistance. In non-diabetic AS patients treated with infliximab, a dramatic reduction in serum insulin levels and improvement in insulin sensitivity after administration of this drug had been demonstrated [50].

The strength of our study was the randomized placebo-controlled design. In Hong Kong, TNF inhibitors are not reimbursed by the government. As a result, most patients in Hong Kong treated with anti-TNF medication need to cover the costs out of pocket. This study was approved by the local ethics committee and was welcomed by patients because free medication was provided to all study patients. Limitations of the trial included the use of surrogate endpoints instead of actual CV events. Second, the sample size was small since this was only a pilot study to obtain preliminary evidence on the effect of golimumab compared with placebo in the prevention of progression of subclinical atherosclerosis and arterial stiffness markers in patients with AS. Based on our results, the sample size needed to show a significant difference between the two groups would be 199 and 113 per arm for outcome based on mean IMT and PWV, respectively. Third, since we have included relatively young Chinese patients with long disease duration who are stable with moderate to severe disease activity, these results may not be generalizable to AS patients from other ethnic backgrounds, with short disease duration or with 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 back to baseline within the time frame of assessment. Fifth, whether longer treatment duration may be required for the process of inflammation suppression on atherosclerotic disease progression in AS patients remains uncertain. Finally, fluctuating disease activity during the course of this study may also contribute to changes in vascular assessment parameters.

Conclusions

These results demonstrate that uncontrolled inflammation may accelerate the progression of atherosclerosis and arterial stiffness in AS patients. Prevention of arterial dysfunction can be prevented by treatment using golimumab for 6 months, independent of changes in metabolic and CV profiles, probably by lowering inflammatory mediators of atherosclerosis.

Rheumatology key messages

- Uncontrolled inflammation may accelerate the progression of atherosclerosis and arterial stiffness in AS patients.
- Golimumab may prevent arterial dysfunction in AS patients.

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Disclosure statement: The authors have declared no conflicts of interest.

References


