Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis?

Lai-Shan Tam¹, George D. Kitas² and Miguel A. González-Gay³

Abstract

Objective. It remains a matter of debate whether TNF-α antagonists have favourable effects on the cardiovascular (CV) system. This systematic review evaluates the effect of TNF-α blockers on the progression of subclinical atherosclerosis and arterial stiffness in patients with inflammatory arthritis.

Methods. A search of the MEDLINE and Web of Knowledge databases was conducted to identify studies into the effect of TNF-α antagonists on subclinical atherosclerosis and arterial stiffness in patients with RA, AS and PsA. Carotid intima-media thickness (cIMT) was used to assess subclinical atherosclerosis. Two methods were used to assess arterial stiffness: pulse wave velocity (PWV) and aortic augmentation index (AIx). Twenty-three studies matching the search criteria were included for analysis.

Results. TNF-α blockers probably are effective in preventing (7/13 studies) or even reversing (5/13 studies) the progression of IMT in patients with RA, AS and PsA who are responding to treatment. With regard to arterial stiffness, PWV was either significantly reduced (7/13 studies) or remained unchanged (6/13 studies) following TNF-α antagonist treatment. Nonetheless, most studies in RA (7/10) reported significant improvement of PWV. AIx remained unchanged in 10 of 13 studies.

Conclusion. The balance of evidence suggests that TNF-α antagonists may have a beneficial effect on preventing the progression of subclinical atherosclerosis and arterial stiffness. It remains unknown whether this effect is specific to TNF-α antagonists or relates to better control of inflammation irrespective of the disease modification strategy by which this is achieved.

Key words: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, intima media thickness, arterial stiffness, TNF-α antagonists, pulse wave velocity, augmentation index.

Introduction

Cardiovascular disease burden in patients with rheumatic diseases

Patients with RA die prematurely compared with the general population [1], primarily because of cardiovascular disease (CVD) [1, 2]. According to a meta-analysis of 14 observational studies (41,490 RA patients), there was a 48% increased risk of incident CVD in patients with RA. The risks of myocardial infarction (MI) and cerebrovascular accident (CVA) were increased by 68% and 41%, respectively [3]. Recent evidence suggests that this phenomenon also occurs in patients with early RA [4–6].

Data regarding CV co-morbidity in patients with SpA are limited. Nonetheless, most studies point towards an increased CV risk in SpA, broadly on a par with the risk level in RA. In patients with PsA, while observational cohort studies and population-based studies have demonstrated an increased mortality in some [7–10] but not all [11, 12] patients, data have consistently indicated an increased susceptibility to CVD and related mortality [13, 14]. Markers of disease activity are associated with an increased CV mortality [15]. Moreover, the prevalence of traditional CV risk factors was higher in patients with PsA [14, 16], probably because of the shared inflammatory...
pathway [16]. Patients with AS are known to have an overall mortality of ~1.6–1.9 times that of the general population and ischaemic disease patients benefit from potent anti-inflammatory treatment. Whether there is an increase in MI [19–22] in AS patients compared with controls has remained controversial, although the prevalence of ischaemic heart disease [14, 22–24] appears increased.

Non-invasive assessment for subclinical atherosclerosis and arterial stiffness

Early diagnosis of atherosclerosis in this population might trigger more aggressive prophylaxis. Structural vascular disease, assessed either as carotid intima media thickening (IMT) or presence of carotid plaque, is a strong indicator of coronary artery disease (CAD) in the general population [25] as well as in patients with RA [26, 27]. Carotid artery US is an established, validated method for visualizing and quantifying atherosclerotic lesions using a non-invasive and repeatable procedure [28, 29]. IMT has been shown to be a significantly superior risk predictor for incident CVD over what was achieved by a model with Framingham risk factors alone in the general population [30], as well as improving CV risk stratification in patients with RA [31] and possibly PsA [32].

Arterial stiffness is increasingly recognized as a surrogate end point for CVD and is associated with the presence of CV risk factors and atherosclerotic diseases [33]. Arterial stiffness can be measured with non-invasive, 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 [34] and predicts future CV events and all-cause mortality in a strong and independent manner [35]. Brachial-ankle PWV (baPWV), calculated as the ratio of the distance between the brachial and the tibial artery divided by the transit time between these two arteries, has been proposed as an additional arterial biomarker of CV risk. baPWV has been shown in cross-sectional comparisons to be associated with CV risk factors and function, as well as CVD, similar to cfPWV [36].

The aortic augmentation index (AIx) is an integrated measure of stiffness and reflection from the periphery, which is determined by left ventricular ejection, PWV and peripheral arterial resistance, and is also related to endothelial dysfunction [37]. It is considered by many researchers to be a sensitive composite index of arterial stiffness [38]. AIx has emerged as a surrogate marker for CVD; a 10% increase in the central AIx is associated with a relative risk of 1.4 for all-cause mortality [39].

Prevalence of subclinical atherosclerosis and arterial stiffness in rheumatic diseases

Evidence of subclinical atherosclerosis including increased IMT [40] was found in RA patients compared with controls, with an overall mean IMT difference of 0.09 mm (95% CI 0.07, 0.11). In addition, subclinical atherosclerosis including carotid or femoral IMT in RA seemed broadly comparable with diseases with well-known increased CV risks, such as diabetes mellitus [41, 42]. Arterial stiffness has also been reported to be increased in RA patients when compared with healthy matched controls and may accelerate the atherosclerotic process directly, thus contributing to the increased CV risk [43–48]. Subclinical atherosclerosis and arterial stiffness have been observed in RA patients with recent disease onset in some [49–53] but not all studies [45, 54, 55], suggesting that the accelerated atherogenic process related to inflammation may precede symptom onset.

PsA patients without overt CVD have evidence of premature atherosclerosis, as indicated by a consistently greater IMT [32, 56–58]. An increased IMT significantly correlates with traditional risk factors [32, 56–58] and disease-related parameters [57, 58]. In patients with AS, an increased prevalence of subclinical atherosclerosis [19, 59, 60] and arterial stiffness [60–64] has been demonstrated in some but not all studies [65–67]. Determinants of IMT and PWV include traditional CV risk factors [62, 64] as well as disease-related parameters [60]. The association of inflammation with IMT remains controversial [59, 68], although the presence of a chronic inflammatory process in these patients may contribute to all stages of atherosclerosis, including early atheroma formation, plaque instability and thrombus development responsible for the development of CV events in these patients. Together, these factors can cause a proinflammatory state and endothelial dysfunction, leading to premature atherosclerosis.

Mechanisms of inflammation in accelerating atherosclerosis in rheumatic diseases

Mechanisms underlying this increased susceptibility remain uncertain and may include an interaction between traditional and novel CV risk factors, enhanced inflammation and oxidative stress emanating from the synovium and adverse CV effects of medications [69]. Monocytes, CD4+ T lymphocytes and most proinflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-18) play a central role in the pathophysiology of the inflammatory arthritis [70] and are involved in the induction and maintenance of the atherosclerotic process (hyperlipidaemia, insulin-resistance, adhesion of white cells to the endothelium, overexpression of some molecules, fatty streak formation and atherosclerotic plaque progression and rupture) [71]. The hypothesis that high-grade systemic inflammation has a central position in driving the increased CV risk in these patients appears attractive, but remains unproven.

During the past decade, TNF-α antagonists have improved the outcome of inflammatory arthritis dramatically. In so doing, most observational studies in RA have demonstrated a reduced risk of ischaemic events with anti-TNF therapy, although such evidence is currently lacking for SpA [72–74]. Moreover, the mechanism by which TNF-α antagonists reduce the CV risk in RA patients is not well understood and remains speculative. The use of surrogate end points instead of actual CV events may provide more evidence on whether rheumatic disease patients benefit from potent anti-inflammatory
treatment such as anti-TNF-α therapy in the prevention of premature atherosclerosis.

Methods

To collect and review the evidence, we performed a systematic literature review using the MEDLINE and Web of Knowledge databases, searching literature published in English from the year of database inception until June 2013, as shown in Fig. 1. Animal studies were excluded. The selected articles included randomized controlled trials (RCTs) and observational studies (prospective and retrospective cohort and case–control studies). The following terms were searched for: (TNF-α antagonist OR anti-TNF OR infliximab OR adalimumab OR etanercept OR golimumab) AND (intima media thickness OR subclinical atherosclerosis OR arterial stiffness OR arterial compliance OR PWV OR augmentation index) AND (RA OR rheumatoid arthritis OR PsA OR AS OR spondyloarthritis OR SpA). The same search terms and limitations were used to search both databases.

The searches yielded 21 citations in MEDLINE and 32 citations in the Web of Knowledge databases. From the combined results, conference abstracts, review articles and duplicates were excluded, leaving 22 articles. The titles and abstracts of all 22 articles were read and unrelated articles were excluded. Further, citation lists from all included studies were searched for additional relevant articles. Articles were deemed relevant if their studies considered the effect of TNF-α antagonists on subclinical atherosclerosis and arterial stiffness in RA, AS and PsA. Based on this search strategy, 23 studies remained and are the focus of this review. It would not be possible or appropriate to calculate the effect sizes of the benefits of anti-TNF therapy in the various analyses due to heterogeneous study designs (case–control studies, observational studies and only a few RCTs); differences in patient populations, disease duration and the length of follow-up and the use of different anti-TNF agents. Notwithstanding these limitations, this review summarizes and discusses data on the vascular effects of four TNF-α antagonists—infliximab, adalimumab, etanercept and golimumab—in patients with RA, AS and PsA. This review focuses on the change in IMT and the two markers of arterial stiffness: PWV and AIX.

Results

Effects of anti-TNF on subclinical atherosclerosis and arterial stiffness in patients with inflammatory arthritis

Intima media thickness

Observational and case–control studies. The effects of TNF-α blockers on the progression of subclinical atherosclerosis in rheumatic diseases are controversial. Progression of IMT has been described in eight RA patients who had maintained high disease activity despite at least 2 years of treatment with infliximab [75] (Table 1). In contrast, six studies in patients with RA demonstrated that IMT either did not change significantly [76–78] or even regressed [79–81] after 6–24 months of treatment with TNF-α blockers. In the two case–control studies showing regression of IMT in the anti-TNF-treated group, IMT remained unchanged in controls [79, 80].

Two other reports that included inflammatory arthritis patients (RA, PsA and AS) [82] and PsA patients [83] also reported IMT reduction in the anti-TNF-treated group while progression was seen in the control group. IMT also remained stable in a recent 5-year follow-up study of AS patients on long-term anti-TNF compared with progression in those who discontinued the use of TNF-α inhibitors [84].

Randomized controlled trials. Two RCTs in early RA patients did not show any significant change in IMT after 6 months of treatment with MTX vs MTX plus infliximab [85] or biologic monotherapy with etanercept, adalimumab or tocilizumab [86]. Another study in patients with AS randomized to receive golimumab or placebo showed that there were no significant differences regarding the change in vascular parameters between the two groups. Nonetheless, a 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 was observed, while the IMT of the golimumab group remained unchanged [87]. Taken together, TNF-α blockers probably are effective in preventing (7/13 studies) or even reversing (5/13 studies) the progression of IMT in patients with RA, AS and PsA who are responding to treatment.

Pulse wave velocity

Rheumatoid arthritis. Data from observational studies regarding the effects of TNF-α blockers on PWV in RA patients were also inconsistent. PWV in five of eight studies was significantly reduced following TNF-α antagonist treatment [43, 77, 82, 88, 89] (Table 2). PWV remained unchanged in three studies [81, 90, 91] following TNF-α antagonist treatment, and only one study included control
<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Disease</th>
<th>Patients, n</th>
<th>Age, years</th>
<th>Disease duration, years</th>
<th>Drug used</th>
<th>Follow-up duration, years</th>
<th>Study design</th>
<th>Effect</th>
<th>Change in IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez-Juanatey et al. [75]</td>
<td>2006</td>
<td>RA</td>
<td>8</td>
<td>50</td>
<td>15</td>
<td>Inf</td>
<td>3</td>
<td>CCS</td>
<td>↑</td>
<td>0.04 mm/year (s.d. 0.038)</td>
</tr>
<tr>
<td>Sidropoulos et al. [76]</td>
<td>2009</td>
<td>RA</td>
<td>12</td>
<td>55</td>
<td>13.3</td>
<td>Ada</td>
<td>1.5</td>
<td>OBS</td>
<td>↔</td>
<td>0.67 (0.4–1) to 0.68 (0.39–12) mm</td>
</tr>
<tr>
<td>Wong et al. [77]</td>
<td>2009</td>
<td>RA</td>
<td>26</td>
<td>49</td>
<td>NA</td>
<td>Inf</td>
<td>1</td>
<td>RCT</td>
<td>↔</td>
<td>P = 0.5</td>
</tr>
<tr>
<td>Gonzalez-Juanatey et al. [78]</td>
<td>2012</td>
<td>RA</td>
<td>34</td>
<td>55</td>
<td>75</td>
<td>Ada</td>
<td>1</td>
<td>OBS</td>
<td>↔</td>
<td>0.65 mm (s.d. 0.16) to 0.69 mm (s.d. 0.21), P = 0.3</td>
</tr>
<tr>
<td>Del Porto et al. [79]</td>
<td>2007</td>
<td>RA</td>
<td>30</td>
<td>55</td>
<td>6.6</td>
<td>Inf</td>
<td>1</td>
<td>CCS</td>
<td>↓</td>
<td>RcIMT: 0.74 mm (s.d. 0.13) to 0.62 mm (s.d. 0.14), P = 0.0001, LcIMT: 0.76 mm (s.d. 0.15) to 0.63 mm (s.d. 0.13), P = 0.001</td>
</tr>
<tr>
<td>Ferrante et al. [80]</td>
<td>2009</td>
<td>RA</td>
<td>40</td>
<td>45</td>
<td>3</td>
<td>Inf</td>
<td>2</td>
<td>CCS</td>
<td>↓</td>
<td>0.737 ± 0.104 mm to 0.625 ± 0.094 mm, P &lt; 0.001</td>
</tr>
<tr>
<td>Kerekes et al. [81]</td>
<td>2011</td>
<td>ERA</td>
<td>8</td>
<td>38</td>
<td>0.5</td>
<td>Ada</td>
<td>0.5</td>
<td>OBS</td>
<td>↓</td>
<td>0.59 mm (s.d. 0.09) to 0.52 mm (s.d. 0.06), P = 0.002</td>
</tr>
<tr>
<td>Angel et al. [82]</td>
<td>2012</td>
<td>RA</td>
<td>15</td>
<td>47</td>
<td>10</td>
<td>Eta</td>
<td>1</td>
<td>CCS</td>
<td>↓</td>
<td>0.002 mm (0.038, 0.039) in TNF-treated group</td>
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<tr>
<td></td>
<td></td>
<td>AS</td>
<td>12</td>
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<td></td>
<td>Ada</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td>PsA</td>
<td>9</td>
<td></td>
<td></td>
<td>Inf</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td>79</td>
<td>43</td>
<td>3</td>
<td>Eta</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Tam et al. [83]</td>
<td>2011</td>
<td>PsA</td>
<td>9</td>
<td>48</td>
<td>7</td>
<td>TNF A [8]</td>
<td>2</td>
<td>CCS</td>
<td>↓</td>
<td>Maximum IMT: decreased at 3 months for groups 1 and 2 after 3 months (both P &lt; 0.05); continued to decrease at 2 years for group 1 only (P &lt; 0.05)</td>
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<tr>
<td>Control</td>
<td></td>
<td></td>
<td>11</td>
<td>52</td>
<td>11</td>
<td>TNF A [8]</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Van Sijl et al. [84]</td>
<td>2013</td>
<td>AS</td>
<td>56</td>
<td></td>
<td></td>
<td>TNF A [8]</td>
<td>5</td>
<td>OBS</td>
<td>↔</td>
<td>+0.012, P-value = 0.061</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>53</td>
<td>0.5</td>
<td>MTX + Inf</td>
<td></td>
<td></td>
<td>↑</td>
<td>+0.060, P-value = 0.025</td>
</tr>
<tr>
<td>Tam et al. [85]</td>
<td>2012</td>
<td>ERA</td>
<td>20</td>
<td>53</td>
<td>0.4</td>
<td>MTX</td>
<td>0.5</td>
<td>RCT</td>
<td>↔</td>
<td>N/A</td>
</tr>
<tr>
<td>Kume et al. [86]</td>
<td>2011</td>
<td>ERA</td>
<td>22</td>
<td>62</td>
<td>0.8</td>
<td>Toc</td>
<td>0.5</td>
<td>RCT</td>
<td>↔</td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>61</td>
<td>0.9</td>
<td>Eta</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>63</td>
<td>0.8</td>
<td>Ada</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Tam et al. [87]</td>
<td>2013</td>
<td>AS</td>
<td>20</td>
<td>36</td>
<td>8</td>
<td>Gol</td>
<td>0.5</td>
<td>RCT</td>
<td>↔</td>
<td>No change in TNF-treated group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>34</td>
<td>11</td>
<td>Placebo</td>
<td></td>
<td></td>
<td>↑</td>
<td>Control: 0.51 mm (s.d. 0.07) at baseline to 0.53 mm (s.d. 0.08) at 6 months, P = 0.044</td>
</tr>
</tbody>
</table>

*aRA patients on DMARDs. **Post hoc analysis of RCT. 'RA patients who refused biologics and received DMARDs. 4RA MTX non-responders. 5RA MTX responders. Patients who had to postpone anti-TNF therapy. 6On TNF-α antagonists for 2 years. 7Discontinued TNF-α antagonists after 3 months of therapy. 8PsA patients on DMARDs. 9On TNF-α antagonists for 5 years. 10Discontinued TNF-α antagonists. 11DMARD-naive early RA patients. ERA: early RA patients; Toc: tocilizumab; Gol: golimumab; Inf: infliximab; Ada: adalimumab; Eta: etanercept; CCS: case-control study; RCT: randomized controlled trial; OBS: observational study; ↑: increase in IMT; ↓: decrease in IMT. The 13 trials included patients with RA only (9), RA + SpA (1), AS only (2) and PsA only (1). Overall, IMT remained unchanged in 7 of 13 studies, improved in 5 of 13 studies and worsened in 1 of 13 studies.
### Table 2: Studies evaluating the effect of TNF-α antagonists on pulse wave velocity in patients with inflammatory arthritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Disease</th>
<th>Patients, n</th>
<th>Age, years</th>
<th>Disease duration, years</th>
<th>Drug used</th>
<th>Follow-up duration, months</th>
<th>Study design</th>
<th>Effect</th>
<th>Change in PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mäki-Petäjä et al. [43]</td>
<td>2006</td>
<td>RA</td>
<td>9</td>
<td>54</td>
<td>NA</td>
<td>Eta</td>
<td>3</td>
<td>OBS</td>
<td>↓</td>
<td>PWV 8.82 m/s (s.d. 2.04) at baseline to 7.94 m/s (s.d. 1.86) at 1 month to 7.68 m/s (s.d. 1.56) at 3 months, ( P = 0.0003 )</td>
</tr>
<tr>
<td>Cypiene et al. [88]</td>
<td>2007</td>
<td>RA</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>Inf</td>
<td>1.5</td>
<td>OBS</td>
<td>↓</td>
<td>Brachial PWV reduced significantly post Inf Compared with control (( P = 0.004 ))</td>
</tr>
<tr>
<td>Komai et al. [90]</td>
<td>2007</td>
<td>RA</td>
<td>15</td>
<td>50</td>
<td>10</td>
<td>Inf</td>
<td>6</td>
<td>OBS</td>
<td>↔</td>
<td>No change</td>
</tr>
<tr>
<td>Wong et al. [77]</td>
<td>2009</td>
<td>RA</td>
<td>26</td>
<td>49</td>
<td>NA</td>
<td>Inf</td>
<td>13</td>
<td>RCT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↓  ( P &lt; 0.01 )</td>
<td></td>
</tr>
<tr>
<td>Kerekes et al. [81]</td>
<td>2011</td>
<td>ERA</td>
<td>8</td>
<td>38</td>
<td>0.5</td>
<td>Ada</td>
<td>6</td>
<td>OBS&lt;sup&gt;#&lt;/sup&gt;</td>
<td>↓ 5.86 m/s (s.d. 1.85) to 5.46 m/s (s.d. 1.52), ( P &gt; 0.05 )</td>
<td></td>
</tr>
<tr>
<td>Angel et al. [82]</td>
<td>2012</td>
<td>RA</td>
<td>15</td>
<td>47</td>
<td>10</td>
<td>Eta</td>
<td>12</td>
<td>CCS&lt;sup&gt;↓&lt;/sup&gt;</td>
<td>↓ 0.54 (0.79) in TNF vs 0.61 (0.81) in control, ( P = 0.004 )</td>
<td></td>
</tr>
<tr>
<td>Mäki-Petäjä et al. [89]</td>
<td>2012</td>
<td>RA</td>
<td>17</td>
<td>58</td>
<td>NA</td>
<td>Ada</td>
<td>2</td>
<td>OBS&lt;sup&gt;↓&lt;/sup&gt;</td>
<td>↓ 9.09 m/s (s.d. 1.77) to 8.63 m/s (s.d. 1.42), ( P = 0.04 )</td>
<td></td>
</tr>
<tr>
<td>Tam et al. [85]</td>
<td>2012</td>
<td>ERA</td>
<td>20</td>
<td>53</td>
<td>0.5</td>
<td>MTX + Inf</td>
<td>6</td>
<td>RCT&lt;sup&gt;↓&lt;/sup&gt;</td>
<td>↓  TNF: -0.78 m/s (s.d. 1.13) vs MTX: 0.18 m/s (s.d. 1.59), ( P = 0.044 )</td>
<td></td>
</tr>
<tr>
<td>Kume et al. [86]</td>
<td>2011</td>
<td>ERA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
<td>62</td>
<td>0.8</td>
<td>Toci</td>
<td>6</td>
<td>RCT&lt;sup&gt;↓&lt;/sup&gt;</td>
<td>↓ Decreased significantly in all three groups No difference in the change in CAVI between groups</td>
<td></td>
</tr>
<tr>
<td>Tam et al. [87]</td>
<td>2013</td>
<td>AS</td>
<td>20</td>
<td>36</td>
<td>8</td>
<td>Gol</td>
<td>6</td>
<td>RCT&lt;sup&gt;↑&lt;/sup&gt;</td>
<td>↑ Control: 12.2 m/s (s.d. 1.6) at baseline to 12.6 m/s (s.d. 1.3), ( P = 0.028 )</td>
<td></td>
</tr>
<tr>
<td>Daien et al. [91]</td>
<td>2013</td>
<td>RA</td>
<td>21</td>
<td>34</td>
<td>11</td>
<td>Placebo</td>
<td>6</td>
<td>OBS&lt;sup&gt;↔&lt;/sup&gt;</td>
<td>↔ No change in the TNF-treated group</td>
<td></td>
</tr>
<tr>
<td>Capkin et al. [92]</td>
<td>2012</td>
<td>AS</td>
<td>28</td>
<td>57</td>
<td>4</td>
<td>Eta</td>
<td>6</td>
<td>OBS&lt;sup&gt;↔&lt;/sup&gt;</td>
<td>↔ Unchanged in both groups</td>
<td></td>
</tr>
<tr>
<td>Mathieu et al. [93]</td>
<td>2013</td>
<td>AS</td>
<td>49</td>
<td>47</td>
<td>12</td>
<td>Inf</td>
<td>12</td>
<td>OBS&lt;sup&gt;↔&lt;/sup&gt;</td>
<td>↔ 6.97 m/s (s.d. 2.03), 6.92 m/s (s.d. 1.81) and 7.10 m/s (s.d. 1.95) at baseline, 6 months and 1 year, respectively, ( P = 0.64 )</td>
<td></td>
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</table>

<sup>a</sup>Post hoc analysis of RCT. <sup>b</sup>DMARD-naive early RA patients. CAVI: cardio-ankle vascular index. CAVI is calculated by the following formula: CAVI = 2\( r \)/dP × lnPs/Pd/PWV<sup>2</sup> where Ps is systolic blood pressure, Pd is diastolic blood pressure, dP is Ps minus Pd, and p is blood density. ERA: early RA patients; Control: patients who had to postpone anti-TNF therapy; Inf: infliximab; Ada: adalimumab; Eta: etanercept; Toci: tocilizumab; Gol: golimumab; RCT: randomized controlled trial; OBS: observational study; ↑: increase in PWV; ↔: no change in PWV; ↓: decrease in PWV. The 13 trials included patients with RA only (9), RA + SpA (1) and AS only (3). Overall, PWV remains unchanged in 6 of 13 studies and improved in 7 of 13 studies. In RA, PWV remains unchanged in 3 of 10 studies (1 case-control study showed no change in the control) and improved in 7 of 10 studies. In three studies that included AS patients only, PWV was unchanged in all studies while one RCT showed a significant increase in PWV in controls.
patients on DMARDs and demonstrated that PWV also remained stable in the control [91]. The post hoc analysis of the first RCT showed that PWV improved in RA patients after treatment with infliximab for 56 weeks [77]. However, the placebo-controlled part of the study was unable to assess the vascular effects of infliximab due to early drop-out of the placebo group.

The RCT by Kume et al. [86] demonstrated that biologics monotherapy (including tocilizumab, etanercept or golimumab) improved arterial stiffness in MTX or biologic-naive early RA patients [86]. In order to address whether MTX alone may result in a similar degree of changes, a third RCT was conducted comparing the vascular effect of MTX plus infliximab with MTX alone in patients with early RA. This study confirmed that 6 months of treatment with MTX plus infliximab 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 CVS risk factors [85]. Overall, potent anti-inflammatory therapy in RA patients using anti-TNF-α and tocilizumab appeared to be effective in improving arterial function as reflected by a reduction of PWV in 7 of 10 studies.

Ankylosing spondylitis. Based on observational studies that included only AS patients [92, 93], PWV remained unchanged after 6 and 12 months of anti-TNF-α therapy. Unfortunately, no control groups were included in the previous trials for comparison. Resembling the change in the mean IMT, the study in AS patients randomized to receive golimumab vs placebo demonstrated a significant progression of PWV in controls after 6 months [from 12.2 m/s² (s.d. 1.6) at baseline to 12.6 m/s² (s.d. 1.3), P = 0.028], while PWV of the golimumab group remained unchanged [87]. 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 [82]. 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, as discussed in the previous section.

Augmentation index
Observational and case-control studies. Different from the results of PWV, the Aix remained unchanged in most (six of eight) of the observational and case-control studies in RA [43, 77, 82, 88, 91, 94] (Table 3). Only one case-control study demonstrated an improvement in the Aix in the TNF-treated group [95] while another study showed that Aix increased significantly over 7 weeks despite anti-TNF treatment [96]. Two observational studies also reported that the Aix remained unchanged after 6 and 12 months of anti-TNF therapy in patients with AS [92, 93]. The Aix in control groups also remained unchanged in the four case-control studies [82, 88, 91, 95].

Randomized controlled trials. Kume et al. demonstrated that biologics monotherapy (including tocilizumab, etanercept or golimumab) improved the Aix in MTX or biologic-naive early RA patients [86], although the results from another group of patients with early RA [85] as well as patients with AS [87] showed that the Aix did not change in both the TNF-treated and control groups. In summary, no change in the Aix was observed in 9/13 studies after anti-TNF therapy.

Discussion
In this literature review, anti-TNF treatment may have a favourable effect on the progression of surrogate markers of atherosclerosis. TNF-α blockers are effective in preventing (7-13 studies) or even reversing (5-13 studies) the progression of IMT in inflammatory arthritis patients who are responding to treatment. More importantly, significant progression of IMT in the control group of patients with active disease not treated with anti-TNF [82-84, 87], and even in the eight RA patients who had maintained a high disease activity despite at least 2 years of treatment with infliximab [75], suggests that uncontrolled inflammation in arthritis patients may accelerate the progression of subclinical atherosclerosis. Measurement of the IMT is a reliable indicator of more advanced, but still subclinical atherosclerosis, and may reflect the cumulative burden of pro-atherogenic factors. As a result, evaluation of the progression of subclinical atherosclerosis by carotid arterial US examination following the treatment of risk factors takes time. Future large-scale, longer-term studies are required to clarify this issue.

The method of obtaining IMT data is also crucial to the validity of the findings when comparing the change in IMT in patients and controls. The process needs to be rigorous and robust, and patients and controls need to be recruited similarly. Moreover, IMT measurement should be conducted according to existing well-validated protocols and in a blinded manner to minimize bias. Unfortunately, information regarding most of these aspects is generally lacking in published studies. The variation in US protocols for determining the IMT between all studies is an important observation, but also complicates interpretation of the individual study results. Still, we think that the differences in ultrasound protocols or in other methodological aspects of the included studies are unlikely to have caused a systematic bias toward under- or overestimation of the change in IMT after anti-TNF therapy.

Overlapping early functional and morphological changes in the vessel can be assessed by characterizing arterial wall stiffness using PWV and pulse wave analysis (PWA). With regard to the change in PWV, potent anti-inflammatory therapy in RA patients using anti-TNF and tocilizumab appeared to be effective in improving arterial stiffness, as reflected by a reduction of PWV in 7 of 10 studies. In patients with RA, one of the possible mechanisms of arterial dysfunction may be related to chronic, low-grade inflammation in the vessels. Using 18F-fluorodeoxyglucose PET to quantify aortic inflammation, RA patients with active disease have increased aortic inflammation comparison with subjects with established, stable CVD, which could be reduced by anti-TNF-α therapy [89]. This effect correlates with the decrease in aortic stiffness measured by PWV, suggesting that subclinical
**Table 3** Studies evaluating the effect of TNF-α antagonists on the Alx in patients with inflammatory arthritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Disease</th>
<th>Patients, n</th>
<th>Age, years</th>
<th>Disease duration, years</th>
<th>Drug used</th>
<th>Follow-up duration, months</th>
<th>Study design</th>
<th>Effect</th>
<th>Change in Alx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Doornum et al. [94]</td>
<td>2005</td>
<td>RA</td>
<td>14</td>
<td>55</td>
<td>8</td>
<td>Eta</td>
<td>1.5</td>
<td>OBS</td>
<td>No change</td>
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<td>Ada</td>
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<tr>
<td>Mäki-Petäjä et al. [43]</td>
<td>2006</td>
<td>RA</td>
<td>9</td>
<td>54</td>
<td>NA</td>
<td>Etn</td>
<td>3</td>
<td>OBS</td>
<td>No change</td>
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<td>Control</td>
<td></td>
<td></td>
<td>No change compared with control</td>
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<tr>
<td>Cypiene et al. [88]</td>
<td>2007</td>
<td>RA</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>Etn</td>
<td>3</td>
<td>OBS</td>
<td>No change</td>
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<td>Control</td>
<td></td>
<td></td>
<td>No change compared with control</td>
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<tr>
<td>Galarraga et al. [95]</td>
<td>2009</td>
<td>RA</td>
<td>26</td>
<td>57</td>
<td>14</td>
<td>Etn</td>
<td>4</td>
<td>OBS</td>
<td>↓ 35% (s.d. 9), 32.5% (s.d. 1) and 32.5% (s.d. 8) at baseline, 2 and 4 months, respectively; ( P=0.025 ) in the TNF-treated group</td>
<td>No change in MTX group</td>
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<tr>
<td>Wong et al. [77]</td>
<td>2009</td>
<td>RA</td>
<td>21</td>
<td>54</td>
<td>4</td>
<td>MTX</td>
<td>13</td>
<td>RCT(^a)</td>
<td>↑ 28.2% (s.d. 10.8) to 31.2% (s.d. 9.4), ( P=0.03 ) for the whole group, ( P=0.01 ) for RA subgroup</td>
<td>( P=0.265 )</td>
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<td></td>
<td></td>
<td>Inf</td>
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<tr>
<td>Pieringer et al. [96]</td>
<td>2010</td>
<td>RA</td>
<td>30</td>
<td>49</td>
<td>10</td>
<td>Inf</td>
<td>2</td>
<td>RCT(^a)</td>
<td>↓ Decreased significantly in all three groups</td>
<td>No change in the change in the Alx between groups</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td></td>
<td></td>
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<tr>
<td>Angel et al. [82]</td>
<td>2012</td>
<td>RA</td>
<td>15</td>
<td>47</td>
<td>10</td>
<td>Eta</td>
<td>12</td>
<td>CCS</td>
<td>↓ −0.5% (s.d. 5.5) in TNF vs −0.3% (s.d. 4.0) in controls, ( P=0.92 )</td>
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<tr>
<td></td>
<td>AS</td>
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<td></td>
<td></td>
<td>Ada</td>
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<td>PsA</td>
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<td>Control</td>
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<tr>
<td>Tam et al. [85]</td>
<td>2012</td>
<td>ERA</td>
<td>20</td>
<td>53</td>
<td>0.5</td>
<td>Etn</td>
<td>6</td>
<td>RCT(^a)</td>
<td>No change in both groups</td>
<td></td>
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<td></td>
<td>MTX + Inf</td>
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<td>MTX</td>
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<tr>
<td>Kume et al. [86]</td>
<td>2011</td>
<td>ERA(^b)</td>
<td>22</td>
<td>62</td>
<td>0.8</td>
<td>Toci</td>
<td>6</td>
<td>RCT(^a)</td>
<td>Decreased significantly in all three groups</td>
<td>No difference in the change in the Alx between groups</td>
</tr>
<tr>
<td>Tam et al. [87]</td>
<td>2013</td>
<td>AS</td>
<td>20</td>
<td>36</td>
<td>8</td>
<td>Gol</td>
<td>6</td>
<td>RCT(^a)</td>
<td>No change in both groups</td>
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<td>Placebo</td>
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<tr>
<td>Dainen et al. [91]</td>
<td>2013</td>
<td>RA</td>
<td>28</td>
<td>57</td>
<td>4</td>
<td>Eta</td>
<td>6</td>
<td>OBS</td>
<td>Unchanged in both groups</td>
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<td>DMARD</td>
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<tr>
<td>Capkin et al. [92]</td>
<td>2012</td>
<td>AS</td>
<td>28</td>
<td>34</td>
<td>8.4</td>
<td>Inf</td>
<td>6</td>
<td>OBS</td>
<td>↑ 21.8% (s.d. 31.6) vs 11.8% (s.d. 18.4), ( P=0.177 )</td>
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<td>Etn</td>
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<tr>
<td>Mathieu et al. [93]</td>
<td>2013</td>
<td>AS</td>
<td>49</td>
<td>47</td>
<td>12</td>
<td>Inf</td>
<td>12</td>
<td>OBS</td>
<td>↓ 19.5% (s.d. 13.1), 20.2% (s.d. 12.8) and 18.3% (s.d. 13.5), respectively, ( P=0.87 )</td>
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<td>Etn</td>
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<td></td>
<td>Ada</td>
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</tbody>
</table>

\(^a\)Post hoc analysis of RCT. \(^b\)DMARD-naive early RA patients. ERA: early RA patients; control: patients who had to postpone anti-TNF therapy; Inf: infliximab; Ada: adalimumab; Eta: etanercept; Toci: tocilizumab; Gol: golimumab; RCT: randomized controlled trial; OBS: observational study; ↑: increased in Alx; ↔: no change in Alx; ↓: decrease in Alx. The 13 trials included patients with RA only (8), RA+SpA (2) and AS only (3). Overall, Alx was unchanged in 9 of 13 studies, increased in 1 of 13 studies and improved in 3 of 13 studies.
vasculitis may contribute towards arterial stiffness in RA patients. On the other hand, no change in PWV after anti-TNF was observed in patients with AS, although a significant increase in PWV was reported in the controls on placebo therapy [87].

In contrast to the change in PWV, no change in Aix was observed in 9/13 studies after anti-TNF therapy. These data suggest that the commonly used surrogate markers of atherosclerotic vascular diseases are not necessarily interchangeable and PWV may be more responsive to change over a short period of time than the Aix. The 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 function, but also microvascular function affect the Aix. Results from these studies suggest that PWV may be a more sensitive marker reflecting changes in predominantly macrovascular function in rheumatic disease patients with chronic inflammation.

Improvement in clinical and laboratory markers of inflammation were observed in all except one study [75], which did not show any improvement in IMT, PWV or the Aix, implying that response to a TNF blocker does not mean that inflammation is fully suppressed in a given individual. Indeed, it has been shown that a notable proportion of AS patients still have MRI-confirmed inflammation even with higher response rates [97]. Whether this may contribute towards the differences in the effects of anti-TNF on the change in PWV in patients with RA compared with AS will need to be addressed in future studies.

A comparison of these studies is difficult due to differences in patient populations, disease duration, length of follow-up and study design across the separate investigations. The differing results concerning the effect of anti-TNF treatment may be attributed to different inclusion and exclusion criteria and, in some case-control studies, poor matching of the intervention and control groups. In the study by Angel et al. [82], the exclusion and inclusion criteria were vague or not implemented fully, as subjects were included who had CAD or hypertension and were smokers, leading to the possibility that other medication may have confounded the results and may be responsible for the significant effects seen.

The conflicting results of these studies may also be explained by the different anti-TNF drugs used and the inflammatory diseases studied. The majority of studies published in the literature included only RA patients (9 of 13 studies for IMT and PWV, 8 of 13 studies for the Aix); more data from patients with SpA are eagerly awaited. It is important to note that different anti-TNF drugs may have differing effects on endothelial and smooth muscle cells and therefore IMT and arterial stiffness. In the RCT by Kume et al. [86], no significant differences between the two anti-TNF agents (adalimumab and etanercept) and tocilizumab were observed with regard to changes in arterial stiffness and IMT. Two previous observational studies [82, 94] also reported no significant differences in the magnitude of the reduction in aortic PWV among the three different TNF-α antagonists (infliximab, adalimumab and etanercept), implying that all three drugs have similar effects on arterial stiffness. Another contributing factor to the diverse results is the relatively small sample size, which may have caused type 2 error (failure to reject the null hypothesis when it is in fact false), with regard to the non-significant results.

Although a substantial number of studies identified beneficial effects in the surrogate markers of atherosclerosis after anti-TNF treatment in patients with inflammatory arthritis, the methodological strength of the existing literature is low. This systematic literature search identified three small-scale RCTs [85–87] (evidence category 1B) and the remaining studies are descriptive studies (evidence category 3). The guidelines for the determination of the level of evidence are provided as supplementary Table S1, available at *Rheumatology* Online. Therefore this review reaffirms that the level of evidence is still insufficient to provide definitive conclusions. Moreover, the evidence of whether these are surrogates for CVD events specifically in these patient populations is currently lacking [98].

This review tried to focus on the effect of anti-TNF therapy in the progression of subclinical atherosclerosis and arterial stiffness. Nonetheless, anti-TNF therapy may not necessarily have a unique advantage, as this may just reflect the benefits of inflammation suppression in general. Data from recent trials demonstrated comparable clinical efficacies and radiological outcomes between conventional combination DMARD and anti-TNF therapy in patients with RA who had active disease despite treatment with MTX [99]. The Swedish Pharmacotherapy (Swefot) study [100] and the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study [101] also compared conventional therapy with TNF inhibitors in patients with active disease despite treatment with MTX. The Swefot study showed no significant difference between infliximab therapy and therapy with SSZ and HCQ at 6 months, but did show a benefit with infliximab at 12 months and better radiographic results after 24 months. The TEAR study included a subgroup of patients who had not had an adequate response to MTX and then received either etanercept or SSZ and HCQ. There was no significant difference in outcome between these two regimens, although treatment with MTX plus etanercept resulted in a statistically significant radiographic benefit compared with oral triple therapy. Moreover, improvement in IMT after 1 year of traditional DMARDs has also been reported in a group of early RA patients [102]. Whether TNF blockers are superior to a combination of traditional DMARDs in preventing the progression of atherosclerosis in patients with inflammatory arthritis needs to be determined by future large-scale RCTs.

**Conclusion**

Many studies linked the suppression of inflammation with a favourable effect on CV surrogate markers, including carotid IMT and PWV. Those studies, although different
in design and comprising low numbers of patients, may be clinically relevant, as they provide indirect evidence to support the inflammatory hypothesis. Obviously, appreciation of shared inflammatory mechanisms in atherosclerosis and rheumatic diseases and placebo-controlled studies with hard CV endpoints are urgently needed for a better understanding of the CV burden in this population. In order to achieve conclusive evidence, long-term well-controlled data and larger patient numbers are needed. At present, differences in the study design and the use of different surrogate markers complicate interpretation. Meanwhile, we advise, in line with previously published European League Against Rheumatism (EULAR) guidelines, adequate CV risk management according to local guidelines and aggressive suppression of inflammation to lower CV risks in these patients with inflammatory arthritis.

Rheumatology key messages
- Uncontrolled inflammation in arthritis patients may accelerate the progression of subclinical atherosclerosis and arterial stiffness.
- TNF-α blockers can prevent progression of intima-media thickness and pulse wave velocity in patients with inflammatory arthritis.

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

Supplementary data
Supplementary data are available at Rheumatology Online.

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