Effect of high dose intravenous ascorbic acid on the level of inflammation in patients with rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a major inflammatory joint disease that causes cartilage destruction, bone erosions, and joint destruction. Oxidative stress is elevated in RA patients implying reactive oxygen species (ROS) are possible mediators of tissue damage. ROS trigger a cascade of events through nuclear factors' activation (NF-kappa B), which up-regulates gene expression of pro-inflammatory cytokines that mediate the immune responses causing inflammation. As ascorbic acid can reduce oxidative stress, decrease production of pro-inflammatory cytokines, and suppress the activation of NF-kappa B, we suggest that millimolar concentration of ascorbic acid may be useful in RA treatment. In our study we analyzed the effect of intravenous vitamin C (IVC) treatment on eleven subjects with RA. Our data suggest that IVC therapy with dosages of 7.5 g - 50 g can reduce inflammation. The level of inflammation as measured by C-reactive protein levels was decreased on average by 44%. Based on our pilot study, we hypothesize that IVC therapy can be a useful strategy in treating RA.

Keywords: Rheumatoid Arthritis; Inflammation; C-Reactive Protein; Intravenous Vitamin C

1. INTRODUCTION

Rheumatoid arthritis (RA) is a major inflammatory joint disease involving damage to cartilage, bone and joints. In severe cases, it can also lead to rheumatoid nodules, vasculitis, heart disease, lung disease, anemia, and peripheral neuropathy. There is no cure for RA at present. Treatment usually beings with non-steroidal anti-inflammatory drugs (ASAIDs) or COX-2 inhibitors, with glucocorticoids or “disease modifying drugs” such as gold and methotrexate being employed in more severe cases. These treatments have limited success and may cause significant adverse effects. Alternative and complementary medicine (CAM) approaches to arthritis include supplementation with gamma-linolenic acid, fish oil (and/or omega 3 fatty acids), antioxidants (such as vitamins C, E, quercetin, and lipoic acid), and dietary adjustments [1]. So far, clinical studies testing these CAM therapies have not demonstrated significant benefits to RA patients [2-7].

RA is thought to be an autoimmune illness. Hallmarks of RA pathology include chronic inflammation and synovial hyperplasia. The synovial membrane, a delicate tissue structure one or two cell layers thick that lines joint cavities, undergoes morphological changes including thickening of intimal lining and formation of invasive tumor-like structures called “pannus” with the onset of RA. In RA patients, T-lymphocytes infiltrate the synovial membrane and produce pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-α) [8], which in turn stimulate release of tissue-destroying matrix metalloproteinases [9], pro-inflammatory enzymes such as Cox-2, and prostaglandins [10-13]. This eventually leads to degeneration of cartilage extracellular matrix. Moreover, oxidative stress and reactive oxygen species (ROS) are elevated in RA patients [14-18], presumably due to the activity of activated macrophages and granulocytes. ROS are known to activate cellular redox sensitive transcription factors, including nuclear factor B (NF-κB), that up regulate genes encoding pro-inflammatory cytokines and enzymes [19-21].

Since NF-κB is a key transcription factor regulating almost all of the pro-inflammatory factors involved in pathogenesis and progression of rheumatoid arthritis [22, 23], it is a potential target for anti-arthritis therapy. The presence of activated NF-κB transcription factors has been demonstrated in cultured synovial fibroblasts [24-26], human arthritic joints [27-32] and the joints of animals with experimentally induced RA [33,34]. Through its up-regulation of IL-1 and TNF-α, NF-κB has an inhibitory effect on cartilage generation (chondro
nfection, form fibroblast-like synoviocytes (FLS) characteristic of the tumor-like pannus [36-38]. In a study using an animal model of RA, NF-κB was required for the induction of inflammatory cytokines in primary synovial fibroblasts, and suppression of NF-κB enhanced apoptosis in the synovium [39]. Thus, NF-κB activation may contribute to hyperplasia by increasing inflammation and inhibiting apoptosis.

Our clinic has long been interested in the use of ascorbate (vitamin C) at millimolar concentrations (attainable via intravenous infusions) to treat illnesses associated with inflammation, including cancer, atherosclerosis, and viral infections [40-48]. At high doses, ascorbate has been shown to reduce the production of pro-inflammatory cytokines and to affect the activation of NF-κB [49-51] and to affect the activation of NF-κB [52-55]. The effect of ascorbate on NF-κB in vitro seems to be concentration dependent: one study indicated that 0.2 mM ascorbate enhanced NF-κB activation in Jurkat T-cells [53], while two other studies using higher ascorbate concentrations showed inhibition of NF-κB in endothelial cells [52] and other human cell types [55]. Ascorbate has other properties that suggest it may be useful in treating rheumatoid arthritis: it is an antioxidant that scavenges ROS [56,57]; it supports collagen formation and enhances extracellular matrix protein synthesis [58,59]. Interestingly, RA patients tend to be vitamin C deficient, with high supplementation doses required to maintain plasma ascorbate at acceptable levels [60]. Other studies show below-normal ascorbate concentrations in synovial fluid of RA patients.

As a first step toward investigating the use of intravenous ascorbate to treat rheumatoid arthritis, we examined our patient database to see how intravenous ascorbate therapy has affected the inflammation marker C-reactive protein (CRP) in arthritis patients.

2. MATERIALS AND METHODS

We searched our database for rheumatoid arthritis patients who 1) were treated with intravenous ascorbate therapy and 2) had pre-treatment and post-treatment assessment of C-reactive protein. Our search yielded eleven subjects, all females from 45 to 69 years old. Key lab parameters for this group are shown in Table 1.

Blood chemistry parameters were obtained using standard medical lab procedures. CRP levels in blood (serum or heparin-plasma) were analyzed using a particle-enhanced immune-turbidimetric assay (CRP Ultra WR Reagent kit, Genzyme) according to manufacturer’s instructions on an automated analyzer (CobasMIRA, Roche Diagnostics). According to the reagent kit manufacturers, an upper limit on the normal CRP range (within two standard deviation of the average) was 1.9 mg/L.

Patients were treated by intravenous vitamin C infusions using our clinic’s standard intravenous ascorbate (IVC) therapy protocol [61]. Briefly, patients were first screened for glucose-6-phosphate dehydrogenase deficiency, as this deficiency can cause hemolysis. Patients with G6PDH deficiency were not given IVC. Subjects were then given IVC at doses of 7.5 g, 15 g or 25 grams infused by slow drip in saline solution. To ensure that patient has adequate renal function, hydration and urinary voiding capacity, baseline lab tests were performed that include a serum chemistry profile and urinalysis. In some cases, additional supplements such as vitamin B6, vitamin C, EPA, and evening primrose oil were also given.

3. RESULTS

The eleven rheumatoid arthritis patients in our study were characterized by moderate to high levels of the inflammation marker CRP accompanying moderate to severe discomfort levels (Table 1). Based on a previously published classification system for CRP as risk factor [62], two of our subjects had moderate (1 - 3mg/L) inflammation while the other nine subjects had high (6.7 mg/L - 44 mg/L) levels of inflammation. The changes in CRP levels after IVC therapy are shown in Table 2.

The average CRP level before treatment was 9.4 ± 4.6 (sd) mg/L, while the average after IVC therapy was 6.4 ± 4.6 (sd) mg/L.

Nine of the eleven subjects (the exceptions being subjects 8 and 11) showed a net decrease in inflammation (as indicated by CRP decreases) during IVC treatment. For these nine subjects, the average CRP decrease was 44 ± 23 (sd)%.

Figures 1 and 2 show examples of how CRP changed over time in four subjects who received the IVC treatments. Subject 6 had twenty IVC treatments of 15 grams each over a 130 day period. Her CRP level decreased steadily from 12.6mg/L to 1.4 mg/L. Subject 5 had similar results with four treatments over a three month period. Subjects 8 and 11 were unusual in that they showed dramatic increases in CRP at certain points in their treatment, with gradual decreases during the remaining periods.

Examining those subjects who showed a net CRP decrease, there is some hint that the effect may be IVC treatment frequency dependent. This is shown in Figure 3, where the drop in CRP is plotted against the average interval between treatments (the number of days of treatment divided by total amount of given treatments).

This is not definitive, but it suggests that further study is warranted. The limitation of our study is that the IVC...
Table 1. Pre-treatment characteristics of eleven rheumatoid arthritis patients analyzed in the present study are given, including age, sex, serum cholesterol (mg/dL), omega-3 and omega-6 fatty acids, \(\Omega_6:\Omega_3\) ratios, weight (lbs), subject rated pain level (1-7), and c-reactive protein (CRP, mg/L) levels.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Cholesterol</th>
<th>Omega-6</th>
<th>Omega-3</th>
<th>Ratio</th>
<th>Weight</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>F</td>
<td>180</td>
<td>26.3</td>
<td>5.4</td>
<td>4.87</td>
<td>165</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>F</td>
<td>190</td>
<td>24.93</td>
<td>4.18</td>
<td>5.96</td>
<td>171.2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>170</td>
<td>23.1</td>
<td>5.5</td>
<td>4.20</td>
<td>145.4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>F</td>
<td>230</td>
<td>320.8</td>
<td>47.1</td>
<td>6.81</td>
<td>197.7</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>F</td>
<td>195</td>
<td>27.12</td>
<td>5.07</td>
<td>5.35</td>
<td>175</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>244</td>
<td>27.19</td>
<td>5.28</td>
<td>5.15</td>
<td>155</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>F</td>
<td>256</td>
<td>24.76</td>
<td>2.28</td>
<td>10.86</td>
<td>180</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>F</td>
<td>210</td>
<td>308.2</td>
<td>62.6</td>
<td>4.92</td>
<td>188</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>177</td>
<td>25</td>
<td>5.2</td>
<td>4.81</td>
<td>160</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>F</td>
<td>274</td>
<td>342</td>
<td>50.3</td>
<td>6.80</td>
<td>217</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>F</td>
<td>178</td>
<td>370.9</td>
<td>52.6</td>
<td>7.05</td>
<td>230</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. C-reactive protein (CRP, mg/L) levels before and after IVC therapy. The number of IVC treatments at each dose, along with the total number of days of therapy, is given. Where applicable, use additional supplements used during therapy are indicated.

<table>
<thead>
<tr>
<th>Subject</th>
<th>CRP before</th>
<th>CRP after</th>
<th>CRP (%)</th>
<th>IVC 7.5 g</th>
<th>IVC 15 g</th>
<th>IVC 25 g</th>
<th>IVC days</th>
<th>Additional supplements used (Oral unless noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>8.7</td>
<td>–21</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>100</td>
<td>EPA, vitamin B6, magnesium</td>
</tr>
<tr>
<td>2</td>
<td>12.3</td>
<td>8.5</td>
<td>–31</td>
<td>1</td>
<td>1</td>
<td>150</td>
<td>1 g Vitamin C orally, EPA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.7</td>
<td>1.9</td>
<td>–30</td>
<td>2</td>
<td>132</td>
<td>2</td>
<td>B-complex, super EPA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6.8</td>
<td>3.9</td>
<td>–43</td>
<td>1</td>
<td>2</td>
<td>800</td>
<td>1 g Vitamin C orally, B-vitamins</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17.2</td>
<td>4.4</td>
<td>–75</td>
<td>4</td>
<td>96</td>
<td>1</td>
<td>EPA, evening primrose oil</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12.6</td>
<td>1.4</td>
<td>–89</td>
<td>20</td>
<td>129</td>
<td>1 g Vitamin C orally, EPA evening primrose oil, coenzyme Q10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>12.1</td>
<td>8</td>
<td>–34</td>
<td>5</td>
<td>177</td>
<td>1 g Vitamin C orally, B-complex, EPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-a</td>
<td>11.9</td>
<td>44.8</td>
<td>+277</td>
<td>3</td>
<td>8</td>
<td>331</td>
<td>B6 IVC injections (1mg), EPA, vitamin D, DHEA</td>
<td></td>
</tr>
<tr>
<td>8-b</td>
<td>44.8</td>
<td>27.1</td>
<td>–40</td>
<td>5</td>
<td>208</td>
<td>B6 IVC injections, EPA, vitamin D, DHEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-c</td>
<td>27.1</td>
<td>14.8</td>
<td>–45</td>
<td>2</td>
<td>1</td>
<td>383</td>
<td>B6 IVC injections, EPA</td>
<td></td>
</tr>
<tr>
<td>8-total</td>
<td>11.9</td>
<td>14.9</td>
<td>24</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>922</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.09</td>
<td>0.99</td>
<td>–53</td>
<td>1</td>
<td>115</td>
<td>DHEA, 1 g vitamin C, vitamins B5, B6, D, EFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>6.7</td>
<td>5</td>
<td>–25</td>
<td>2</td>
<td>1</td>
<td>206</td>
<td>B6 IVC injections, 500 mg Vitamin C, EFA, Bplex IV</td>
<td></td>
</tr>
<tr>
<td>11-a</td>
<td>7.6</td>
<td>3.1</td>
<td>–59</td>
<td>16</td>
<td>187</td>
<td>B-complex IV, B6 IV infusion, EPA, vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-b</td>
<td>3.1</td>
<td>13.1</td>
<td>320</td>
<td>10</td>
<td>99</td>
<td>B6 IVC, evening primrose oil, EPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-c</td>
<td>17.6</td>
<td>13.1</td>
<td>–26</td>
<td>5</td>
<td>55</td>
<td>B-plex, B6 IVC, evening primrose oil, EPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 11-total</td>
<td>7.6</td>
<td>13.1</td>
<td>72</td>
<td>31</td>
<td>341</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Finally, since CRP levels can be affected by body mass, we examined the subjects’ weight change during treatment. In most cases, patient weight change was less than six percent. There was no correlation between CRP levels administration protocol was different for different patients.
4. CONCLUSIONS

Chronic inflammation underlies the pathology of rheumatoid arthritis. Decreasing inflammation and oxidative stress may provide protection for regenerating cartilage within the joint. Control of inflammation in patients with RA is also the important goal when it comes to the reduction of cardiovascular risk in these patients [63]. Our data, while preliminary in nature, suggest that IVC therapy may reduce inflammation as measured by C-reactive protein levels. The possible mechanism of this effect may be the suppression of NF-κB, which regulates the production of pro-inflammatory molecules (cyclooxygenase-2 matrix, metalloproteinase MMP-3, MMP-9, TNF-α, IL-1b, and other pro-inflammatory cytokines). The modulatory effects of high dose IVC may also be on the level of oxidative stress seen in these patients.

Based on this pilot study, we hypothesize that IVC therapy be a useful strategy in treating RA, and that more
research into this possibility is warranted. Future clinical studies should also include measurements of pro-inflammatory cytokine levels.

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REFERENCES


