

BRIEF REPORT

Interleukin-6 as an Inflammatory Mediator and Target of Therapy in Chronic Periaortitis

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Objective. Chronic periaortitis (CP) usually responds to glucocorticoids, but some patients have glucocorticoid-refractory disease or contraindications to glucocorticoid therapy. This study was undertaken to evaluate treatment with the anti-interleukin-6 receptor (anti-IL-6R) antibody tocilizumab in 2 patients with CP, one with refractory disease and the other with contraindications to glucocorticoids, and to assess IL-6 levels in an additional cohort of patients with CP.

Methods. Both patients were given intravenous tocilizumab (8 mg/kg) once every 4 weeks for 6 months. Serum IL-6 was measured in 22 patients with active CP and 16 healthy controls. Tissue IL-6 expression was assessed by confocal microscopy in biopsy specimens obtained from 6 patients with CP.

Results. In the first patient, whose disease was refractory to various immunosuppressive treatments, tocilizumab added to ongoing therapy with prednisone and methotrexate allowed prednisone withdrawal and induced resolution of symptoms, acute-phase reactant normalization, and reduction in ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake on positron emission tomography. The patient experienced a relapse 7 months later and was successfully retreated with tocilizumab. In the second patient, who was unable to tolerate glucocorticoids because of psychiatric side effects, tocilizumab monotherapy induced sustained clinical and laboratory

remission, ¹⁸F-FDG uptake disappearance, and CP shrinkage. Serum IL-6 levels were significantly higher in patients with active CP than in controls ($P < 0.0001$), and IL-6 was abundantly expressed in biopsy specimens from CP patients, particularly by T cells, B cells, histiocytes, fibroblasts, and vascular smooth muscle cells.

Conclusion. Tocilizumab may be a therapeutic option for CP. The systemic and tissue up-regulation of IL-6 in CP, together with the clinical benefit of IL-6R blockade observed in our 2 patients, suggest that IL-6 may contribute to CP pathogenesis.

Chronic periaortitis (CP) is a rare disorder characterized by a fibroinflammatory tissue that spreads from the adventitia of the abdominal aorta and the iliac arteries into the retroperitoneum, where it frequently entraps the ureters (1). Traditional definitions of CP are “idiopathic retroperitoneal fibrosis” when the aorta is of a normal size, and “inflammatory abdominal aortic aneurysm” or “perianeurysmal retroperitoneal fibrosis” when the aorta is dilated. Early studies proposed that CP results from an allergic reaction to atherosclerotic plaque antigens (2), but recent reports indicate that it can be a manifestation of a systemic autoimmune or immune-mediated disorder, given its prominent acute-phase reaction and its association with autoimmune diseases and the HLA-DRB1*03 allele (1). In some patients, CP involves not only the abdominal aorta and the iliac arteries, but also the thoracic aorta and the epiaortic arteries, mimicking large vessel vasculitides (1).

Glucocorticoids are the cornerstone of therapy for CP. They usually induce rapid resolution of symptoms, normalization of acute-phase reactants, and CP shrinkage (3). Combinations of glucocorticoids and immunosuppressive agents such as cyclophosphamide, azathioprine, and methotrexate have also been used as

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first-line therapy (4,5), but their superiority to glucocorticoids alone is yet unproven. In addition, the role of these immunosuppressants in patients with refractory or glucocorticoid-dependent disease, or in those who cannot tolerate glucocorticoids, is unclear. For such cases, new therapeutic alternatives are needed.

Interleukin-6 receptor (IL-6R) blockade with tocilizumab has proven effective for many autoimmune or inflammatory diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, and large vessel vasculitides (6). Herein, we describe the successful use of tocilizumab in 2 patients with CP, one whose disease was refractory to various immunosuppressive therapies, and the other with contraindications to glucocorticoids. Using samples obtained from our CP cohort, we also demonstrate that serum IL-6 levels are high in active CP, and that IL-6 is abundantly expressed by different cell types in biopsy specimens from CP patients.

PATIENTS AND METHODS

Patient selection. Between March 2007 and February 2011, 18 patients with CP were seen at the Rheumatology Unit of Reggio Emilia Hospital (Reggio Emilia, Italy). They all received conventional treatment with glucocorticoids, alone or in combination with immunosuppressants (methotrexate or azathioprine) or tamoxifen. Three patients who had either refractory disease or contraindications to glucocorticoids received biologic agents as second-line therapies. In particular, one patient with refractory disease was successfully treated with infliximab (see ref. 7). A second patient (patient 1 in the present study) had refractory disease that failed to respond to infliximab and abatacept. This patient then received tocilizumab, and given the excellent results observed, tocilizumab was used for an additional patient (patient 2 in the present study) who was not able to tolerate glucocorticoids.

Diagnosis of CP, imaging, and laboratory evaluations. CP was diagnosed by contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI), following commonly accepted criteria (8). Neither of the 2 patients described here underwent retroperitoneal biopsy. ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET)-CT was performed in both cases to assess disease activity. Vascular/perivascular ¹⁸F-FDG uptake was graded using a 4-point scale ranging from 0 to 3, where 0 = no uptake, 1 = low-grade uptake (lower than liver uptake), 2 = intermediate-grade uptake (similar to liver uptake), and 3 = high-grade uptake (higher than liver uptake). CP was considered to be active if the uptake grade was ≥ 2 (9).

Secondary forms of retroperitoneal fibrosis were ruled out as previously described (3). The patients underwent routine laboratory examinations, including evaluation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels and a panel of autoantibodies (3). We also measured serum IL-6 and soluble IL-6R (sIL-6R) levels using an enzyme-linked immunosorbent assay (R&D Systems). Normal

values for serum CRP, IL-6, and sIL-6R levels were <0.5 mg/dl, <4.5 pg/ml, and <80.1 ng/ml, respectively.

Written informed consent was obtained from both patients before they received tocilizumab. The study was approved by the local ethics committee.

Measurement of serum IL-6 in a cohort of CP patients and healthy controls. To assess IL-6 levels in a larger CP cohort, we obtained sera from 22 consecutive patients with CP recruited at the Nephrology Unit of the University Hospital of Parma between January 2008 and April 2011. All patients had newly diagnosed and active CP and were untreated. The control group consisted of 16 age- and sex-matched healthy subjects. Sera were obtained at the time of diagnosis and stored at -80°C until used. Serum IL-6 was measured using a Bio-Rad Luminex assay (Life Science Group). All samples and standards were analyzed in duplicate. We used a Luminex 100 instrument for cytokine detection and examined the results using Bio-Rad Manager Software version 4.0 (Life Science Group). Differences in IL-6 levels were assessed by Mann-Whitney test.

Tissue expression of IL-6 in biopsy specimens from patients with CP. In order to assess IL-6 tissue expression, we retrieved the retroperitoneal biopsy specimens obtained from 6 CP patients who were followed up at the Nephrology Unit of the University Hospital of Parma. We performed immunohistochemistry using an anti-IL-6 primary polyclonal antibody (catalog no. AF-206-NA; R&D Systems) and an anti-IL-6 monoclonal antibody (catalog no. ab9324; Abcam) on 5- μm -thick paraffin-embedded slides. The reaction was revealed with 3,3'-diaminobenzidine, and the slides were counterstained with Harris' hematoxylin.

We also performed confocal microscopy analysis by incubating the histologic sections with either the above-mentioned anti-IL-6 primary polyclonal antibody or an isotype control (normal goat IgG control; goat IgG) (catalog no. AB-108-C; R&D Systems) and each of the following primary monoclonal antibodies: anti-CD3 (1:50), anti-CD20 (1:200), anti-CD68-KP1 (1:800), antivimentin (1:500), antidesmin (1:1,000), and anti- α -smooth muscle actin (anti- α -SMA; 1:100) (all from Ventana Medical Systems). The IL-6 and isotype control reactions were revealed by a tetramethylrhodamine probe (tetramethylrhodamine donkey anti-goat IgG) (catalog no. A11057; Invitrogen), while the other proteins were revealed by a fluorescent probe (fluorescein isothiocyanate-conjugated goat anti-mouse IgG) (catalog no. AP124F; Chemicon). The immunofluorescence samples were observed using a confocal system (LSM 510 META scan head integrated with the Axiovert 200M inverted microscope; Carl Zeiss) with a 63 \times oil objective. The images were acquired in multitrack mode, using consecutive and independent optical pathways.

RESULTS

Patient 1. The patient, a 66-year-old woman, was admitted to the Rheumatology Unit of Reggio Emilia (Reggio Emilia, Italy) in February 2004 because of abdominal pain and systemic symptoms (anorexia, weight loss, and fatigue). The ESR and CRP level were 114 mm/hour and 4.5 mg/dl, respectively. Abdominal CT

scan showed a periaortic and periiliac soft tissue density mass, extending from the origin of the renal arteries to the bifurcation of the common iliac arteries, consistent with CP. FDG-PET revealed grade 3 ^{18}F -FDG uptake not only at the level of the abdominal aorta and iliac artery, but also around the thoracic aorta (the initial imaging findings were reported previously in a clinical vignette [10]). All screening tests for secondary retroperitoneal fibrosis were negative.

Treatment with prednisone 1 mg/kg/day (55 mg/day) was started, and the dose was slowly tapered during the ensuing months. One year later, PET-CT scan revealed a reduction in ^{18}F -FDG uptake (grade 2) at both the thoracic and abdominal aorta levels. However, despite the addition of methotrexate (administered orally at ~ 0.3 mg/kg/week [15 mg/week]) as maintenance therapy, the patient experienced repeated relapses with the reappearance of systemic manifestations and an elevation in inflammatory markers upon tapering of the prednisone dose below 12.5 mg/day. She therefore continued to take prednisone 12.5 mg/day plus methotrexate for 2 years, and developed hypertension and multiple vertebral fractures.

In October 2007, PET-CT scan showed grade 1 ^{18}F -FDG abdominal aorta uptake, while grade 3 uptake was found at the level of the thoracic aorta. Infliximab (5 mg/kg administered intravenously every 8 weeks) was added to methotrexate (15 mg/week) and prednisone (12.5 mg/day). However, during the 1-year period of infliximab infusions, the patient again experienced a relapse when the prednisone dose was tapered below 12.5 mg/day. Infliximab was thus withdrawn. A further therapeutic attempt with abatacept (500 mg administered intravenously every 4 weeks for 6 months) also failed to achieve remission or to allow prednisone tapering.

In April 2010, while the patient was still taking methotrexate (15 mg/week) and prednisone (12.5 mg/day), her ESR and CRP level were 69 mm/hour and 0.88 mg/dl, respectively. IgG4 levels were 14 mg/dl (normal range 3–201 mg/dl). PET-CT scan revealed grade 3 ^{18}F -FDG uptake at the level of the ascending thoracic aorta. Tocilizumab (8 mg/kg administered intravenously every 4 weeks for 6 months) was given as add-on therapy. After the first infusion, the ESR and CRP level rapidly normalized, and 3 months later the patient started to taper prednisone by 2.5 mg/day each month until complete withdrawal, without relapse of disease manifestations.

Figure 1A shows the patient's ESR and CRP, serum IL-6, and sIL-6R levels during tocilizumab ther-

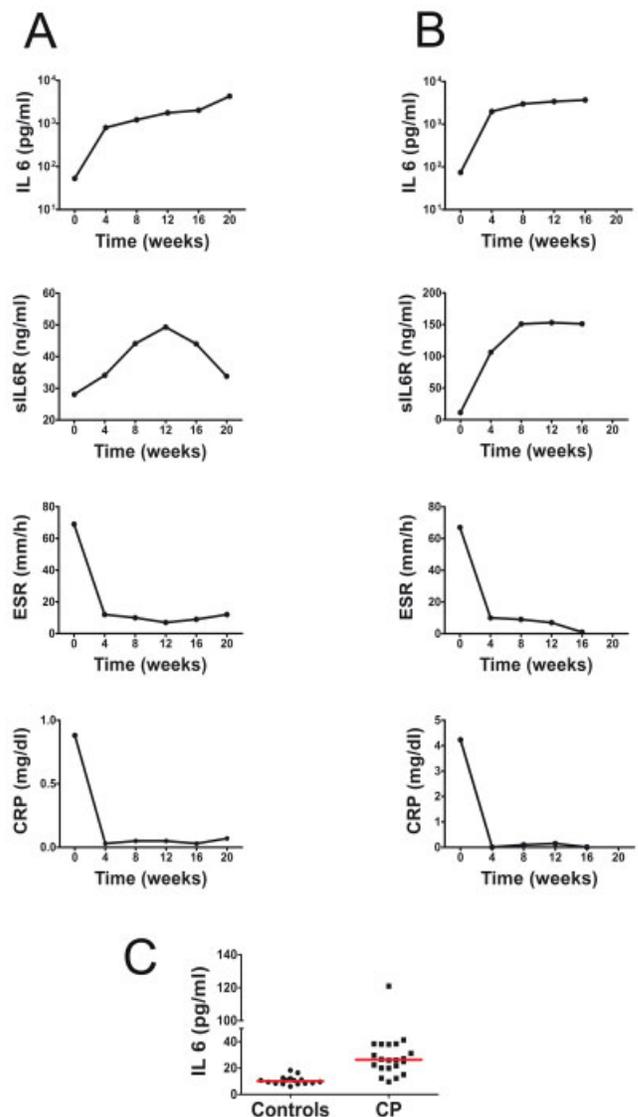


Figure 1. Findings in 2 individual patients with chronic periaortitis (CP) undergoing tocilizumab therapy and interleukin-6 (IL-6) levels in a cohort of patients with CP. **A** and **B**, Serum IL-6 levels, serum soluble IL-6 receptor (sIL-6R) levels, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels in patient 1 (**A**) and patient 2 (**B**) during tocilizumab therapy. Values on the x-axis are the time elapsed since the first tocilizumab infusion. **C**, Serum IL-6 levels in a cohort of 22 untreated patients with newly diagnosed active CP and 16 age- and sex-matched healthy controls. IL-6 levels were significantly higher in CP patients than in controls ($P < 0.0001$ by Mann-Whitney test). Symbols represent individual patients; horizontal lines show the median. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/art.38032/abstract>.

apy. In November 2010, after the sixth infusion, her disease was in clinical and laboratory remission while

she was receiving only methotrexate (15 mg/week), and PET-CT scan showed grade 1 thoracic aorta uptake. Tocilizumab was stopped.

In June 2011, anorexia, weight loss, fatigue, and proximal arthromyalgia reappeared. ESR and CRP level were 120 mm/hour and 1.86 mg/dl. IL-6 and sIL-6R levels were 2,375.8 pg/ml and 29.9 pg/ml, respectively, comparable to those recorded at the last tocilizumab infusion. PET-CT scan again demonstrated grade 3 ^{18}F -FDG uptake at both the ascending and abdominal aorta levels. Tocilizumab was resumed at the same dosage, and methotrexate (15 mg/week) was continued. In December 2011, after 6 infusions (every 4 weeks), the patient was symptom free, and the ESR and CRP level were 16 mm/hour and 0.04 mg/dl, respectively. CT scan showed disappearance of the abdominal periaortic cuff, while thoracic periaortitis was unchanged in size but had low contrast enhancement.

Patient 2. The patient, a 55-year-old man, presented in March 2010 with fatigue, lumbar and abdominal pain, and constipation. The ESR was 98 mm/hour, and the CRP level was 7.01 mg/dl. Thoracoabdominal CT scan showed a perivascular cuff of soft tissue density surrounding the infrarenal abdominal aorta, the common iliac arteries, and the inferior mesenteric artery, consistent with CP. The serum IgG4 level was 80 mg/dl (normal range 3–201 mg/dl). Prednisone (initial dose of 1 mg/kg/day) suppressed clinical symptoms and normalized inflammatory markers within 1 month, but induced irritability, insomnia, and anxiety up to frank psychosis with hallucinations and suicidal ideation, necessitating prednisone withdrawal within 4 months. The psychotic manifestations subsided completely upon treatment withdrawal.

In February 2011, the patient was admitted to the Rheumatology Unit of Reggio Emilia Hospital because of recurrent systemic manifestations, abdominal pain, and constipation. The ESR and CRP level were 67 mm/hour and 4.23 mg/dl, respectively. Abdominal CT (Figures 2A and C) confirmed the presence of CP involving the lower abdominal aorta, both common iliac arteries, and the inferior mesenteric artery. PET-CT scan revealed grade 3 ^{18}F -FDG uptake around the abdominal aorta and the iliac arteries, particularly on the right (Figure 2E). The patient refused to resume prednisone; therefore, we decided to use tocilizumab alone (8 mg/kg administered intravenously every 4 weeks for 6 months). After the first infusion, ESR and CRP normalized (to 10 mm/hour and 0.01 mg/dl), while abdominal pain and systemic manifestations gradually

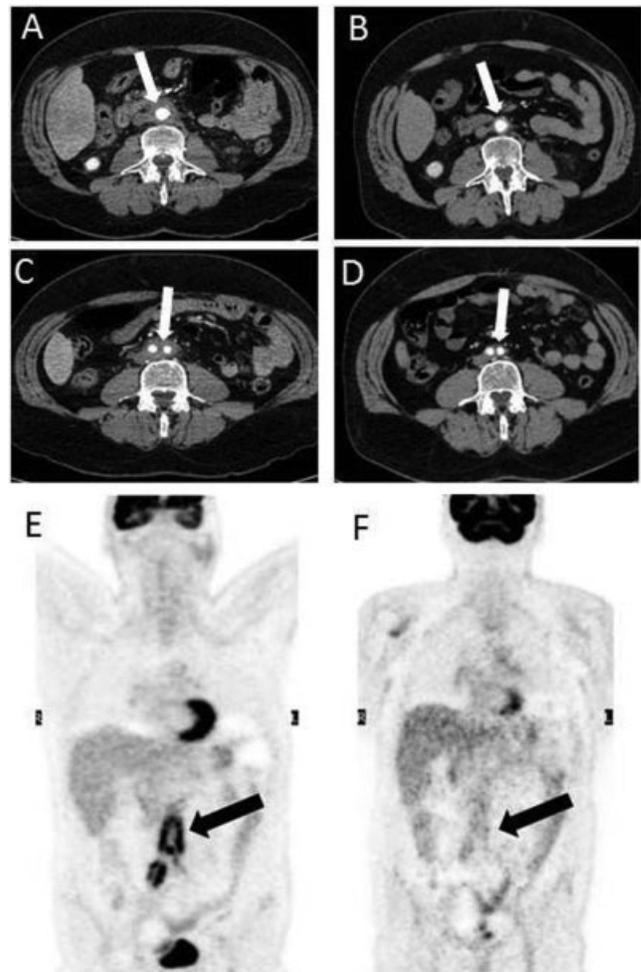


Figure 2. Computed tomography (CT) and positron emission tomography (PET) findings in patient 2 before and after tocilizumab therapy. **A** and **C**, Contrast-enhanced abdominal CT scans at the level of the infrarenal abdominal aorta (**A**) and common iliac arteries (**C**) before treatment with tocilizumab, showing a periaortic and periiliac cuff of soft tissue density (arrows). **B** and **D**, Contrast-enhanced abdominal CT scans at the level of the infrarenal abdominal aorta (**B**) and common iliac arteries (**D**) after tocilizumab monotherapy, showing marked shrinkage of the masses at both sites (arrows). **E** and **F**, PET scans showing periaortic and periiliac uptake of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) (arrows) before tocilizumab therapy (**E**) and disappearance of ^{18}F -FDG uptake after tocilizumab therapy (**F**).

improved and completely disappeared after the fourth infusion. Figure 1B illustrates the patient's ESR and CRP, IL-6, and sIL-6R levels during tocilizumab therapy. In July 2011, at the end of the treatment course, abdominal CT scan showed a marked shrinkage of CP (Figures 2B and D), and PET-CT scan showed complete disappearance of ^{18}F -FDG uptake (Figure 2F). Remis-

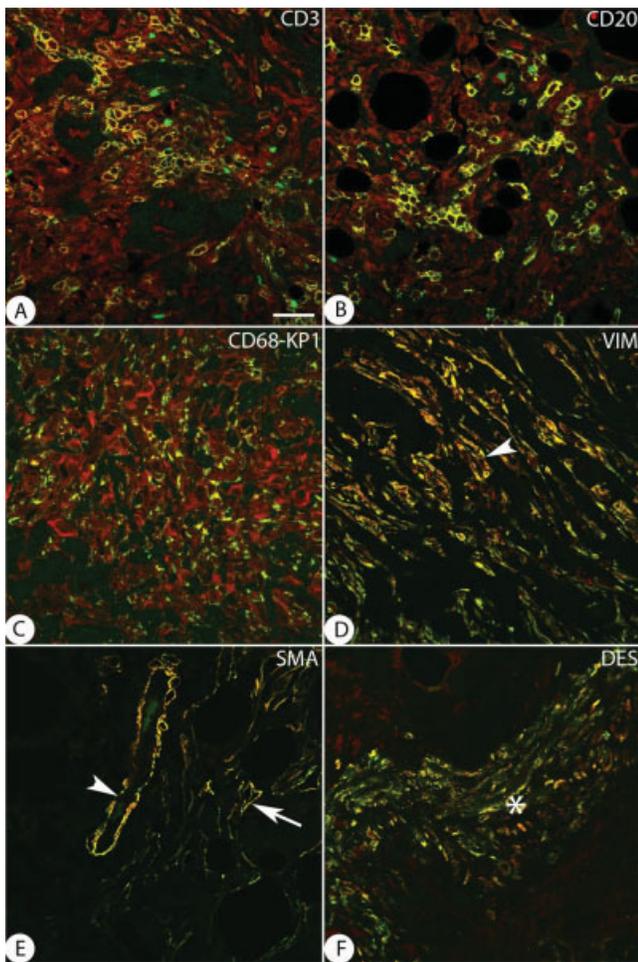


Figure 3. Confocal microscopy analysis of interleukin-6 (IL-6) tissue expression in biopsy specimens from patients with chronic periaortitis (CP). Representative images of IL-6 expression in retroperitoneal biopsy specimens obtained from 6 patients with active CP are shown. Green staining indicates the various proteins investigated, red staining indicates IL-6, and yellow staining indicates signal superimposition of red and green staining. **A–C**, Intense IL-6 positivity within CD3+ T lymphocytes (**A**), CD20+ B lymphocytes (**B**), and CD68+ histiocytes (**C**). **D**, Marked IL-6 expression in spindled fibroblasts/myofibroblasts (**arrowhead**) identified using vimentin (VIM). **E**, Marked IL-6 expression in both the smooth muscle cells of a medium-sized blood vessel (**arrowhead**) and myofibroblasts (**arrow**) identified using α -smooth muscle actin (α -SMA). **F**, Marked IL-6 expression in smooth muscle cells of a larger blood vessel tunica media (**asterisk**) identified using the muscular marker desmin (DES). Original magnification $\times 63$; bar = 30 μ m.

sion maintenance with methotrexate (20 mg/week) was started. At the last followup visit, in July 2012, the patient was asymptomatic, acute-phase reactants were normal, abdominal CT findings were unchanged, and PET-CT scan showed no pathologic uptake.

Serum IL-6 levels and tissue IL-6 expression in CP. To explore whether IL-6 levels are actually elevated in active CP, we used serum samples from 22 patients with newly diagnosed, untreated CP and 16 healthy controls. Serum IL-6 was significantly higher in CP patients than in controls, with median values being ~ 2.5 -fold higher in the former group (26.36 pg/ml versus 10.15 pg/ml; $P < 0.0001$) (Figure 1C). IL-6 levels did not differ between patients with and those without systemic symptoms ($P = 0.695$), and no correlations were found between serum IL-6 level and ESR ($P = 0.567$), CRP level ($P = 0.280$), or serum creatinine level ($P = 0.294$). Likewise, IL-6 levels did not differ between patients with and those without ureteral obstruction ($P = 0.872$). We also evaluated the presence of thoracic periaortitis. Of the 22 patients, 5 (23%) had thoracic periaortitis, 16 (73%) had no thoracic involvement, and results were not available for 1 (4%). IL-6 levels tended to be higher in the patients with thoracic periaortitis. In this group, the median IL-6 level was 38.0 pg/ml (range 19.9–120.9), while in the group without periaortitis it was 25.4 pg/ml (range 9.6–56.0). This difference was not statistically significant ($P = 0.149$), although the small sample sizes of the 2 groups must be acknowledged.

We next assessed IL-6 expression in retroperitoneal biopsy samples obtained from 6 patients who were newly diagnosed as having CP. Immunohistochemistry with both monoclonal and polyclonal antibodies showed that numerous spindle-shaped cells (most likely fibroblasts) and mononuclear inflammatory cells were IL-6 positive (results not shown). Confocal microscopic analysis showed intense IL-6 positivity within CD3+ T cells, CD20+ B cells, and CD68+ histiocytes. Interestingly, fibroblasts and myofibroblasts (identified using vimentin and α -SMA, respectively) also markedly expressed IL-6, and so did vascular smooth muscle cells (identified using α -SMA and desmin) (Figure 3). Isotype control staining was consistently negative (results not shown).

DISCUSSION

The treatment of CP is largely based on the use of glucocorticoids, but there is an unmet need for alternative therapies, particularly for glucocorticoid-refractory disease, glucocorticoid-dependent patients, and those who cannot tolerate glucocorticoids. A panoply of immunosuppressive agents, including mycophenolate mofetil (5), cyclophosphamide, and azathioprine (4) have been successfully used in CP, but no controlled studies have demonstrated their glucocorticoid-sparing role or effectiveness in refractory disease. We have

recently reported on the use of rituximab (11) and infliximab (7) in anecdotal patients with refractory disease, but these data need further validation.

In this study, we used tocilizumab to treat CP based on the following considerations. First, tocilizumab is effective in different inflammatory conditions, including large vessel vasculitides (12,13), which share with CP large artery involvement and pronounced adventitial inflammation. Second, IL-6 plays a key pathogenetic role in experimental models of systemic sclerosis and graft-versus-host disease. These conditions are hallmarked, as is CP, by an intense fibrosing response and have anecdotally been reported to respond to tocilizumab (6). Third, CP is characterized by a marked acute-phase reaction, which might be driven by IL-6 similarly to other inflammatory disorders.

In both of our patients, CP responded to tocilizumab. In the first patient, whose disease was refractory to multiple medications, adjunctive tocilizumab only proved able to induce remission while allowing glucocorticoid withdrawal. The second patient received tocilizumab as monotherapy; therefore, his response is clearly attributable to tocilizumab. Importantly, neither patient reported tocilizumab-related side effects. Since the study included only 2 cases, these data cannot be generalized and need confirmation in larger studies.

In our patients, we assessed disease activity clinically and by PET-CT. PET-CT is a useful tool in the evaluation of CP metabolic activity. However, it is expensive and not available in all centers, so CT and MRI are routinely used to follow up CP patients. These provide excellent morphologic details and reliably assess changes in size in CP but probably have a lower ability (as compared with PET) to assess disease activity (1,9).

Serum IL-6 levels were high in both of our patients during active disease. To extend this observation, we measured serum IL-6 in a cohort of patients with newly diagnosed, untreated CP and in healthy controls, and found significantly higher levels in CP patients. Next, we found that IL-6 was also highly expressed in biopsy specimens from CP patients. Interestingly, the main sources of IL-6 production were not only inflammatory cells such as lymphocytes and histiocytes, but also myofibroblasts and vascular smooth muscle cells. Taken together, these findings indicate a marked systemic and local up-regulation of IL-6 in CP.

Similar to other studies (13), we observed an increase in serum sIL-6R and IL-6 levels during tocilizumab therapy. Experimental evidence suggests that sIL-6R levels increase as the formation of tocilizumab/sIL-6R immune complexes delays the elimination of

sIL-6R, whereas IL-6 probably increases because its clearance is impaired by IL-6R blockade and not because its synthesis is enhanced (14). Consistent with these findings, inflammatory markers and disease activity remained suppressed in our patients, suggesting that IL-6 signaling was inhibited and inflammation was curtailed.

The clinical benefit of IL-6R blockade in our 2 patients, along with the elevated serum levels of IL-6 and its pronounced expression in biopsy specimens from CP patients, suggest that this cytokine may be a key player in CP. IL-6 is a pleiotropic molecule, and its functional effects may be relevant for CP pathogenesis. IL-6 enhances the production of acute-phase proteins and induces systemic manifestations, which are often found in active CP (1). IL-6 also induces activation and differentiation of B cells, which are abundant in the pathologic tissue of CP, where they form the core of the inflammatory aggregates, sometimes organized in germinal centers (11). IL-6 also promotes differentiation of CD4+ cells into IL-17-producing T helper cells, and activates CD8+ cells (6). T cells, particularly CD4+ T cells, are the most frequent cell type in CP inflammatory infiltrates, although their T helper polarization is still unknown. Finally, IL-6 induces fibrosis, a key feature of CP, through different mechanisms, including fibroblast-to-myofibroblast differentiation, collagen deposition, and inhibition of metalloproteinase activity (15).

In conclusion, IL-6R blockade using tocilizumab may be a viable therapeutic option for CP. The clinical benefits observed in our 2 cases and the observed up-regulation of IL-6 in the serum and pathologic tissue of CP patients suggest that IL-6 may contribute to disease pathogenesis. Although encouraging, our preliminary results require validation in larger trials.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Salvarani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Vaglio, Catanoso, Pipitone, Corradi, Salvarani.

Acquisition of data. Vaglio, Catanoso, Spaggiari, Magnani, Macchioni, Pulsatelli, Nicastro, Becchi, Salvarani.

Analysis and interpretation of data. Vaglio, Versari, Boiardi, Salvarani.

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