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Brief report

Noninfectious aortitis: Experience with tocilizumab in a regional hospital[☆]



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ABSTRACT

Objectives: Describe patients with noninfectious aortitis and their response to treatment in a regional hospital.

Methods: Review of patients with noninfectious aortitis, diagnostic technique used and immunosuppressive therapy received.

Results: We report 8 patients (7 women and one man) diagnosed with aortitis by positron emission tomography (PET). The mean age was 69 years (interquartile range [IQR] 62–72.2). Three months of treatment with tocilizumab improved symptoms, erythrocyte sedimentation rate and C-reactive protein level ($P < .001$ and $P < .012$, respectively) in the 6 patients in whom it was used.

Conclusions: Tocilizumab was an effective and safe treatment in those patients diagnosed with aortitis refractory to steroids and conventional immunosuppressive therapy.

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Aortitis no infecciosa: experiencia con tocilizumab en un hospital comarcal

RESUMEN

Objetivos: Describir pacientes con aortitis no infecciosa y su respuesta al tratamiento de un hospital comarcal.

Métodos: Revisión de pacientes con aortitis no infecciosa, técnica diagnóstica utilizada y tratamiento inmunosupresor recibido.

Resultados: Se encontraron 8 pacientes (7 mujeres y un hombre) diagnosticados de aortitis mediante tomografía por emisión de positrones (PET). La mediana de edad fue de 69 años (IQR 62–72,2). Tocilizumab (TCZ) mejoró los síntomas, la VSG y la PCR a los 3 meses del tratamiento ($p < 0,001$ y $p < 0,012$, respectivamente) en los 6 pacientes en que se utilizó.

Conclusión: TCZ fue eficaz y seguro en los pacientes que fueron refractarios a esteroides y a otros tratamientos inmunosupresores.

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Introduction

Non-infectious aortitis is a rare entity which often remains undetected. Symptoms may be highly varied from headaches or typical symptoms of rheumatic polymyalgia (RPM) to other less common symptoms including dyspnoea, fever, and claudication in lower limbs. On occasions it may be observed within the context of a recognized great blood vessel (giant cell arteritis [GCA] or Takayasu's disease), associated with a systemic disease (essentially an IgG4 related disease) in isolation or associated with RPM. As a result, these possibilities have to be considered for the administration of appropriate treatment.

It is often the case that immunosuppressive treatment with steroids, methotrexate or azathioprine is insufficient, and this obliges us to seek new therapeutic options. In this study we present our experience in a regional hospital.

Material and methods

A retrospective search of patients diagnosed with non-infectious aortitis was made during the years 2010–2016 and the following data were collected: age, sex, initial symptoms on diagnosis, temporal artery biopsy, diagnostic technique used, time from onset of symptoms to diagnosis made by positron emission tomography (PET), time elapsed to the initiation of tocilizumab (TCZ) in patients considered refractory to standard treatment with steroids and immunosuppressive drugs, and final drug dose. An initial recording of erythrocyte sedimentation rate (ESR)/C reactive protein (CRP) level was made and 3 months after remission

was achieved. Remission was defined as an improvement in clinical symptoms and normalization of ESR and CRP.

Statistical analysis

The description of the quantitative variables was made using the median and the interquartile range (IQR) and the comparison of variables was carried out with the Wilcoxon test.

Results

We found 8 patients: 7 women and one man. The mean age of presentation was 69 years (IQR 62–72.2). The most common clinical symptom at onset was RPM, headache and asthenia. Six of the 8 patients presented with parietal headache or parieto-occipital headache of recent onset. All except patient 8 underwent a temporal artery biopsy (Table 1). In patient 5 the bilateral temporal artery biopsy tested negative. Out of all of the patients, only patient 7 tested positive. The ESR median at onset and end was 78.5 (IQR 67.7–102) and 10.9 (IQR 4.5–14.7), respectively ($P < .001$) and the median of the CRP (mg/dl) at onset and at the end was 7.6 (IQR 2.9–12.3) and .7 (IQR .5–1.8), respectively ($P < .012$). The median of delayed diagnosis was 19.5 (IQR 6–49) months. The median steroid dose where a resurgence of symptoms was observed was of 17.5 mg (IQR 13.1–23.7) days of prednisone. All the patients except patient 6 received concomitant treatment with disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate was used in all patients except patient 6 to a maximum dose of 25 mg weekly. Patients 1 and 5 were also treated with azathioprine at doses of 100 and

Table 1
Patient characteristics.

Sex	Age at onset of symptoms	Symptoms	Temporal artery biopsy	Initial ESR/CRP (mg/dl)	Final ESR/CRP (mg/dl) ^a	Time to diagnosis ^b	Steroid dose (mg)/FAME (mg) ^c	Diagnostic technique	Time to initiation of tocilizumab ^d
1 Woman	73	RPM, asthenia	Negative	114/14.54	15/3	50	Prednisone 20 MTX 20 Imurel 100	PET	3 months
2 Woman	74	RPM, dyspnoea, fronto-parietal headache, asthenia	Negative	65/2.79	7/12	21	Prednisone 20 MTX 20	PET (angio-NMR Negative)	26 months
3 Man	69	RPM, parietal headache	Negative	70/7.89	9/8	12	Prednisone 30 MTX 25	PET	0 months
4 Woman	62	RPM, TMJ pain, parieto-occipital headache	Negative	83/13.08	14/7	1	Prednisone 15 MTX 15	PET	Not initiated
5 Woman	58	RPM, LL claudication, asthenia, temporal headache	Negative (bilateral)	105/1.86	6/5	46	Prednisone 5 Imurel 150 Dolquine 400	PET (PET 2012 Negative)	10 months
6 Woman	69	Parietal headache, asthenia, fatigue, dyspnoea	Negative	67/7.27	2/6	50	Prednisone 25 No DMARDs	PET	.5 months
7 Woman	70	RPM, TMJ pain, fever, asthenia, temporo-parietal headache	Positive	93/9.89	4/4	18	Prednisone 15 MTX 15	PET	1 month
8 Woman	62	RPM, asthenia	Not carried out	74/3.07	30/2	4	Prednisone 12.5 MTX 25	PET	Not initiated

TMJ: temporomandibular joint; LL: lower limbs; DMARDs: disease-modifying drugs; MTX: methotrexate; PET: positron emission tomography; RPM: rheumatic polymyalgia.

^a After 3 months of treatment when remission was obtained.

^b From the onset of symptoms (in months).

^c Steroid and DMARDs doses at the beginning of the refractory process.

^d From diagnosis of aortitis by PET.

Table 2

Classification criteria of giant cell arteritis (GCA) from the American College of Rheumatology (ACR) 1990.

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| <ol style="list-style-type: none"> 1. Age at onset >50 years 2. Headache of recent onset 3. Abnormalities in temporal artery such as enlargement and pain on palpation or reduced pulse 4. ESR >50 mm/h 5. Abnormal temporal artery biopsy showing vasculitis with mononuclear cells or granulomatous inflammation, usually with giant cells |
|---|

ESR: erythrocyte sedimentation rate.

The presence of three or more of the five criteria accounts for the diagnosis of GCA.

150 mg daily, respectively. The final diagnostic test was the PET. In patient 2 the PET was compatible with aortitis, and the angiographic magnetic resonance (angio-MR) was negative. The median time from diagnosis of the disease to treatment initiation with TCZ was 2 months (IQR. 4–14). Of the 8 patients in this series, 6 required treatment with TCZ.

Patients 4 and 8 did not start treatment with TCZ: patient 4 due to complications (bilateral pulmonary thromboembolism) and 8 due to being controlled with methotrexate and prednisone. Treatment with TCZ was suspended in patients 1 and 2 due to major improvement after 6 months, but had to be re-established due to a worsening of clinical symptoms and analytical tests and to the PET results, with good posterior control. There were no secondary adverse effects to the use of TCZ.

Discussion

In this review, 7 out of 8 patients presented with clinical symptoms of RPM, with ESR over 50 mm/h and aged over 50. Six of them had concomitant headaches, which led to them meeting three criteria, sufficient, according to the *American College of Rheumatology* (ACR) of 1990, for the diagnosis of GCA,¹ although only one of them (patient 7) tested positive in the temporal artery biopsy (Table 2). Since it is known that in the GCA there exists the possibility of involvement of great supraaortic vessels and the aorta itself, demonstration of aortitis by PET enabled us to consider the diagnosis in all of our cases, ruling out the possibility of overlapping with non-infectious idiopathic aortitis or aortitis associated with other processes.² Due to all of the above we deduced there remained a need for updating GCA criteria of the ACR to adjust the sensitivity and specificity of current diagnostic resources.^{2–4}

PET appears to be a good tool for diagnosis, especially in the very initial stages of the disease, to assess response to treatment and/or disease recurrence.⁵ Several studies suggest, given its specificity and predictive positive value, that it is superior to CT and angio-MR.^{6,7} However, it remains unclear how useful it is in long-term follow-up of the disease activities, which in several cases, despite

observing clinical and analytical improvement, metabolic activity continues to be present.^{5–7}

TCZ has demonstrated its efficacy in GCA after results obtained from the GiACTA⁸ study. Studies have been published which demonstrate the efficacy of TCZ in non-infectious aortitis even when other biological therapies have been attempted previously, such as the anti-tumour necrosis factor alpha (antiTNF- α).⁹ Treatment with antiTNF- α has been used in an attempt to control remission maintenance induced by steroids in GCA, with poor results.¹⁰ In our series TCZ was a safe and effective treatment in the cases where it was administered.

Conclusion

In this series PET was the definitive diagnostic test for aortitis and GCA in all patients. Corticosteroids and conventional immunosuppressive treatment was insufficient for good control of the disease in the majority of patients. Treatment with TCZ was effective and safe in this series of patients when non-infectious aortitis refractory to treatment with corticosteroids and DMARDs.

Conflict of interests

The authors have no conflict of interests to declare.

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