Takayasu arteritis: anti-TNF therapy in a Brazilian setting

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ABSTRACT

The aim of this study was to describe clinical features and response to different therapeutic interventions, including anti-tumor necrosis factor (TNF) agents, in a case series of Takayasu arteritis (TA) from Brazil. A retrospective observational chart-review study was performed including all patients meeting the American College of Rheumatology TA classification criteria followed at the rheumatology outpatient clinic of a Brazilian university hospital. Fifteen patients were included, of which 14 (93.3%) were females, with a mean age of 29.6 years at diagnosis. Systemic hypertension (60.0%) and abolished upper limb pulses (53.3%) were the most common clinical features at the diagnosis. Subclavian and carotid arteries were the most commonly affected vessels. Twelve patients (80.0%) did not achieve sustained remission on therapy with corticosteroids alone and received immunosuppressive agents including methotrexate, azathioprine and cyclophosphamide. Surgical intervention was necessary and performed in 53.3% of cases. Three cases (20.0%) were refractory to corticosteroid plus diverse immunosuppressive therapy and were treated with anti-TNF agents, all of them with disease remission. In conclusion, a significant proportion of TA cases are refractory to traditional therapy. The use of anti-TNF agents may become a possible therapy for these patients.

Keywords: Takayasu arteritis, epidemiology, therapeutics, tumor necrosis factor-alpha.

INTRODUCTION

Takayasu arteritis (TA) is a chronic large-vessel vasculitis, of which etiology is still unknown. It mainly involves the aorta and its major branches, which leads to inflammatory thickening and damage of vessel walls, with subsequent stenosis or aneurysm formation. The annual incidence of TA is about 2.6 per million individuals, and it mainly affects young women.[1] Although treatment with glucocorticoids can control disease activity, TA usually pursues a recurrent course, and thus the majority of patients will become chronically corticoid-dependent, with several adverse consequences, despite the use of immunosuppressive agents as corticoid-sparing drugs.[2,3] For difficult cases, anti-tumor necrosis factor (TNF) agents have been proposed as promising therapy.[4] Due to the disease rarity, knowledge about the clinical course and therapeutic approaches in TA remains exclusively based on case series from different countries. Therefore, we intend to describe clinical, laboratory, radiographic manifestations and treatment responses in a group of TA patients from a university referral center in Brazil, including the recent use of anti-TNF agents.

METHODS

We performed a retrospective study including all patients followed at the rheumatology outpatient clinic of Universidade Federal de Santa Catarina (UFSC) between July, 2007 and

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July, 2008 who met the American College of Rheumatology classification criteria for TA.[5] Charts of all patients were reviewed for demographic, clinical, treatment, radiological and laboratory data. Disease activity was assumed when patients had systemic signs or symptoms such as fever, malaise, arthritis or elevation of acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) that were not attributable to another condition, or new onset of signs and symptoms of vascular insufficiency, or new vascular lesions on imaging examination in previously not affected territories. Remission was defined as resolution of clinical and laboratory findings of disease activity, in the absence of new lesions on imaging studies, during a period of at least 6 months in a therapeutic regimen with prednisone doses equal to or lower than 10 mg/day. All patients were contacted by phone and a personal interview was scheduled to check data and obtain written informed consent. The Institutional Ethics Committee approved this study protocol (number 278/07), which was performed according the principles of the Declaration of Helsinki. Data were stored and analyzed by Epidata 3.1 and Epidata Analysis 1.1.

RESULTS

Fifteen patients were included. There were 14 females (93.3%) and 1 male (6.6%). The mean age at diagnosis was 29.6 (15-53) years and mean disease duration was 5.7 (1-15) years. The most frequent finding at diagnosis was systemic hypertension (60.0%), followed by abolished upper limb pulses (53.3%), subclavian bruit (40.0%), arthralgias (40.0%), fever (40.0%), headache (33.3%), unequal blood pressure in upper limbs (33.3%), absence of lower limb pulses (26.7%), weight loss (20.0%), carotidynia (20.0%), syncope (13.3%) and abdominal bruit (13.3%).

Conventional angiography was performed in 7 patients (46.7%), while magnetic resonance (MR) imaging of aorta and its main branches was performed in 10 patients (66.7%) and angiotomography imaging in 4 patients (26.7%). Carotid and renal vascular Doppler ultrasonography (US) were performed in 9 (60.0%) and 4 (26.7%) patients, respectively. Subclavian and carotid arteries were more frequently affected, in 90.0% and 56.0% of cases, respectively.

Mean ESR (Westergren) at presentation was 43 (15-118) mm/h, and mean CRP (nephelometry) was 5.6 (0-121) mg/L. Mean values of hemoglobin (12.5[9,7-14.3] g/dL), total leukocyte count (9210[3900-15600] per mm^3), platelet count (278,000[135,000-705,000] per mm^3), creatinine (0.8[0.5-1.9] mg/dL), glucose (81[67-98] mg/dL), total cholesterol (186[154-262] mg/dL), HDL cholesterol (46[30-66] mg/dL), LDL cholesterol (109[78-188] mg/dL) and triglycerides (124[76-254] mg/dL) were within normal ranges.

Regarding treatment, all patients (100.0%) received initial therapy with a prednisone dose of 1 mg/Kg/day, which was progressively tapered after resolution of disease activity. Immunosuppressive agents were added when there was no response to glucocorticoid therapy or if disease reactivation occurred during steroid dose reduction, and we observed that twelve (80.0%) patients finally needed a second-line agent. Methotrexate (MTX) was used by 9 (60.0%) patients, azathioprine (AZA) by 4 (26.7%) and cyclophosphamide (CPP) by two patients (13.3%). Surgical procedures were performed in eight patients (53.3%), consisting mainly of different angioplasty procedures, most commonly in renal arteries (2 cases).

Three patients (20.0%) were refractory to these drug associations. In two cases (CSBW and ALPM) prednisone could not be reduced to less than 20 mg/day because CRP values were persistently higher than 6 mg/L despite the use of second-line agents (MTX p.o. 25 mg/week in the first case, AZA 3 mg/kg/day followed by CPP 1 g/m^2/month i.v. in the second case) and the disease progressed with worsening of renal arteries stenosis in both patients. In one case (TZ), prednisone could not be reduced to less than 60 mg/day, because of persistently high CRP values despite the use of second-line drugs (MTX 25 mg/week, followed by AZA 3 mg/kg/day), and the disease progressed with new stenoses in both carotid arteries and left subclavian artery. These three patients received the anti-TNF agent infliximab (IFX) 5 mg/kg i.v. in periodic infusions, which led to disease control improvement in all cases. Prednisone doses were reduced to 10 mg/day (TZ and CSBW) or discontinued (ALPM) at the time of this study, after a period of six to ten months of IFX therapy. Individual data are presented in Table 1.

DISCUSSION

It can be observed that female predominance and disease onset around the third decade, as described in our series, are worldwide common features in TA series.[6-12] The frequency of main clinical features is also relatively similar in different studies, especially hypertension[8,13] and decreased upper limb pulses[9]. However, differently from previous reports, more recent observations have emphasized that traditional TA therapy has severe limitations, leading to guarded prognostic in an expressive number of patients.[9] Our results showed that few sustained remission occurred with corticosteroids as a single-drug therapy, and most patients (80.0%) had to use

Table 1
Demographic, clinic and treatment data of 15 consecutive TA patients

Initials	Gender	Age (years)	Disease duration (years)	Clinical features at presentation	Second-line agents	Evolution after second-line agents	Anti-TNF agent
CSBW	F	21	2	Hypertension, carotid bruit, BP difference	MTX	High CRP, worsening of renal artery stenosis	IFX
ALPM	F	31	15	Hypertension	AZA, CPP	High CRP, worsening of renal artery stenosis	IFX
TZ	F	17	4	Hypertension, absent upper limb pulse,	MTX, AZA	High CRP, new stenosis in carotid and subclavian arteries	IFX
ALS	F	39	5	Hypertension, carotid bruit, absent upper limb pulse, BP difference	MTX		
MRB	F	34	3	Hypertension, carotid bruit			
DAC	F	17	4	Hypertension, carotid bruit	AZA		
SA	F	50	1	Absent upper limb pulse	CPP		
CAMP	F	40	13	Absent upper limb pulse			
JM	M	10	5	Absent upper limb pulse, carotid bruit	MTX		
IL	F	22	10	Absent upper limb pulse, BP difference	MTX		
MG	F	19	9	Absent upper limb pulse	MTX		
VLP	F	35	7	Hypertension			
VLL	F	47	1	Hypertension absent upper limb pulse, BP difference	MTX		
GACL	F	33	1	Carotid bruit, BP difference	MTX, AZA		
EH	F	51	3	Hypertension	MTX		

F = female; M = male; BP = blood pressure; MTX = methotrexate; AZA = azathioprine; CPP = cyclophosphamide; CRP = C-reactive protein; TNF = tumor-necrosis factor; IFX = infliximab.

immunosuppressive agents after disease recurrence. Other studies also described that second-line agents were necessary in the majority of cases (60% to 73%).[6,9] We reported a high rate of surgical procedures (53.3%), which we considered a marker of disease severity, that is similar to recent data from Italy (50%)[8] and North America (48%).[9] Also, a significant proportion of our patients were refractory to therapy with corticosteroids plus immunosuppressive drugs. Considering that cumulative activity and silent deterioration of vascular lesions in TA are considered predictors of bad prognosis, disease activity surveillance that includes noninvasive imaging tests on a regular basis have been considered important and aggressive treatments for severe cases that present persistent activity have been advocated.[10] Hence, there is a clear need for more efficacious therapies for TA.

Many therapeutic options have been tried in severe TA. A recent Brazilian open-label study revealed mycophenolate mofetil as an efficacious steroid-sparing agent in TA.[14] Also, excellent responses with infliximab therapy were described by Hofmann *et al.* (remission in 14 of 15 patients)[15] and Maksimowicz-McKinnon *et al* (remission in 10 of 11 patients).[9] Our results represent the first case series from Brazil reporting good results with anti-TNF agents in TA refractory disease. In our series, these refractory cases consisted of three patients with persistently high CRP levels and worsening or onset of new vascular lesions despite therapy with prednisone plus one or two immunosuppressant agents. A question that remains to be answered is whether patients with progressive disease in the absence of inflammatory markers can also benefit from anti-TNF therapy.

In conclusion, treatment with corticosteroids and traditional immunosuppressive drugs did not succeed in halting the progression of a significant proportion of cases of TA in this case series from Brazil. In this subgroup of difficult TA patients, the use of anti-TNF agents may become a possible therapy.

REFERÊNCIAS

REFERENCES

1. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol 2002; 55:481-6.
2. Maksimowicz-McKinnon K, Hoffman GS. Takayasu arteritis: what is the long-term prognosis? Rheum Dis Clin North Am 2007; 33:777-86.
3. Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. Curr Opin Rheumatol 2005; 17:16-24.
4. Tanaka F, Kawakami A, Iwanaga N, Tamai M, Izumi Y, Aratake K *et al*. Infliximab is effective for Takayasu arteritis refractory to glucocorticoid and methotrexate. Intern Med 2006; 45:313-6.
5. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM *et al*. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990; 33:1129-34.
6. Sato EI, Hatta FS, Levy-Neto M, Fernandes S. Demographic, clinical, and angiographic data of patients with Takayasu arteritis in Brazil. Int J Cardiol 1998; 66 Suppl 1:S67-70.
7. Ruige JB, Van Geet C, Nevelsteen A, Verhaeghe R. A 16-year survey of Takayasu's arteritis in a tertiary Belgian center. Int Angiol 2003; 22:414-20.
8. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G *et al*. Takayasu's arteritis: A study of 104 Italian patients. Arthritis Rheum 2005; 53:100-7
9. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2005; 56:1000-9.
10. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. Circulation 1994; 90:1855-60.
11. Jain S, Kumari S, Ganguly NK, Sharma BK. Current status of Takayasu arteritis in India. Int J Cardiol 1996; 54 Suppl:S111-6.
12. Lupi-Herrera E, Sánchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis Clinical study of 107 cases. Am Heart J 1977; 93:94-103.
13. Sharma S, Rajani M, Talwar KK. Angiographic morphology in nonspecific aortoarteritis (Takayasu's arteritis): a study of 126 patients from north India. Cardiovasc Intervent Radiol 1992; 15:160-5.
14. Shinjo SK, Pereira RM, Tizziani VA, Radu AS, Levy-Neto M. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. Clin Rheumatol 2007; 26:1871-5.
15. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004; 50:2296-304.