Long-term efficacy and improvement of health-related quality of life in patients with Takayasu's arteritis treated with infliximab

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Abstract

Objective

To explore the efficacy in the long-term and the impact on Health Related Quality of Life (HRQOL) of infliximab in patients suffering from Takayasu's arteritis (TA).

Methods

Clinical data were retrospectively collected in 15 patients with TA. Evaluation of Medical Outcomes Study Short Form 36 (SF-36) questionnaires was made at baseline and at the last follow-up in 10 patients continuing infliximab at the last follow-up.

Results

Follow-up after initiation of infliximab was 71±44 months (range 10-162). Remission at the last follow-up was noted in 11/15 (73.3%). Significant reduction in BVAS score was noted at the last follow-up [from 4.0 (1–16) to 3.0 (0–9), p=0.003]. Significant steroid dose reduction was recorded [from 10 mg/day (0–50) to 2.5 mg/day (0–15), p=0.005)]. Steroid suspension occurred in 5/11 responder patients. Inflammatory markers were normalised in about two thirds of the patients. Radiological disease activity was assessed in 13/15 during infliximab therapy, with evidence of improvement in 2/13, stable disease activity in 9/13, and worsening in 2/13. No relevant side effects or severe infections were recorded during the whole follow-up under infliximab. One patient stopped infliximab at the third infusion for acute reaction. HRQOL in patients with TA was impaired, with major involvement of physical domains [(body pain (BP) and global health (GH)]. Infliximab significantly improved HRQOL, in particular BP (40.0±32.3 vs. 67.2±27.6, p=0.035), GH (31.2±21.5 vs. 54.9±21.1, p=0.007) and Vitality (VT) (47.0±28.7 vs. 67.0±20.3, p=0.01) domains.

Conclusion

Infliximab determined a sustained clinical improvement in the long-term in TA, with significant benefits on HRQOL.

Key words

Takayasu, arteritis, infliximab, quality of life

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Introduction

Takayasu's arteritis (TA) is a rare, chronic panarteritis of the aorta with its major branches appearing commonly at a young age (1). New or worsened abnormal physical findings consistent with vasculitis, presence of constitutional features, elevated acute-phase reactants, and new vessel involvement in imaging are major features of an active disease. However, assessment of disease activity and damage in TA may be problematic given the chronic, indolent disease course and lack of specific laboratory and imaging findings (2). Moreover, Health Related Quality of Life (HRQOL) in patients with TA is significantly impaired in comparison with healthy controls (3). In addition, HRQOL is comparable to that observed in patients with chronic polyarthritis (4), while it is worse than that observed in diabetes mellitus, hypertension, and coronary artery disease (3). Conventional therapy consists of glucocorticoids which may be associated with other immunosuppressive drugs. However, some patients fail to achieve remission with conventional treatment (5, 6). Higher mRNA gene expression of TNF-α, IFN-γ, IL-2, IL-3, IL-4, elevated expression of IL-12 mRNA after stimulation of the cells with lipopolysaccharide and lower expression of IL-10 transcripts as compared to controls have been demonstrated by study of pro-inflammatory cytokine transcripts of peripheral blood mononuclear cells from TA patients, suggesting a role of these cytokines in the pathogenesis of this disease (7). The efficacy of anti-tumour necrosis factor-α (TNF-α) in patients with difficult-to-treat TA preliminary observed in some observational studies and case series also supported the animal and *in vitro* studies (8-13). In our retrospective study, a very long-term follow-up in TA patients treated with infliximab has been reported, highlighting both the clinical efficacy and the effects on the HRQOL by Medical Outcomes Study Short Form 36 (SF-36) Health Survey and European Quality of Life-5 dimensions (EQ5D) derived score.

Patients and methods

All patients fulfilled the American College of Rheumatology (ACR) or the Ishikawa criteria modified by Sharma, or both (14, 15). Data were collected retrospectively in three Italian Rheumatologic Centres. Demographic, clinical and laboratory variables are presented in Table I. These included sex, age, age at onset, age at diagnosis, imaging supporting the diagnosis, clinical features and Birmingham Vasculitis Activity Score (BVAS) before infliximab initiation, co-morbidities, previous treatments for TA, infliximab starting dose, concomitant immunosuppressors and other medications, including antiaggregants, and steroid dose. Notably, BVAS was used to measure the clinical disease activity, since it is a widely accepted index for systemic vasculitis, even if a really good tool to assess large-vessel vasculitis is still lacking at present (16). Interestingly, two patients (n. 3, and n. 5, Table I) had an older age at diagnosis than expected for TA classification criteria (15), although consistent with previously published epidemiologic observations in TA patients (17).

Infliximab was used according to the best clinical practice of the referent clinician.

Clinical disease activity and relapse were defined by the presence of new onset or worsening of two or more of: *i*) systemic features, such as fever, musculoskeletal pain (no other cause identified); *ii*) elevated erythrocyte sedimentation rate; *iii*) features of vascular ischaemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain (carotidodynia), asymmetric blood pressure in either upper or lower limbs (or both); *iv*) typical angiographic features (1). Notably, as regards the last point, *i.e.* typical features observed at conventional angiography, computed tomography (CT) angiography and/or magnetic resonance angiography (MR angiography) and/or 18F-fluorodeoxyglucosepositron emission tomography with CT (FDG CT/PET) and/or colour Doppler ultrasound (CDUS) were used in the majority of patients instead of conventional angiography (Table I). Fibrinogen was not considered in the laboratory variables because not available in all the patients. Radiological disease activity was evaluated in 14/15 patients before

Table I. Characteristics of the patients.

Patient	Age (at start of IFX; at last F-up)	Age at disease onset (years)	Age at disease diagnosis (years)	Co-morbidities	Previous treatments	Concomitant medications	Prednisone or equivalents (mg/day)	Imaging supporting the diagnosis	BVAS	IFX starting dose
1	22; 26	21	22	Iron-deficiency anaemia, migraine, recurrent genital candidosis	-	MTX, CyA	50	CDUS, MR angiography	7	5 mg/kg every 6 wks
2	21; 29	20	20	_	GC, MTX	MTX, Antiaggregants	10	CDUS, MR angiography	2	4 mg/kg every 8 wks
3	65; 71	64	65	dyslipidemia, mild aortic insufficiency	GC, MTX, CyA	CYA, Antiaggregants	5	CDUS, MR and CT angiography, CT/PET	5	3 mg/kg every 8 wks
4	37; 42	31	31	surgically removed pheochromocytoma, type 2 DM, multifactorial anaemia, OP, dyslipidemia	GC	MTX, Antiaggregants	10	CDUS, MR angiography, conventional angiography, brain MRI	16	5 mg/kg every 8 wks
5	62; 66	59	61	anxiety/depression, OP, dyslipidemia, COPD	GC, MTX, CYC, AZA	MTX, AZA, Antiaggregants+ Anticoagulant	0	CDUS, CT/PET	7	5 mg/kg every 8 wks
6	40; 43	32	32	_	GC, MTX, CyA, ADA	MTX, Antiaggregants	0	CDUS, CT/PET	4	6 mg/kg every 6 wks
7	19; 27	18	18	_	GC, MTX	MTX, Antiaggregants	50	_	4	3 mg/kg every 6 wks
8	32; 40	25	26	_	GC, MTX, AZA, MMF	MTX, Antiaggregants	50	MR angiography	4	4 mg/kg every 6 wks
9	21; 26	21	21	_	GC, MTX	MTX, Antiaggregants	50	CT/PET	4	3 mg/kg every 6 wks
10	28; 29	27	28	_	GC, MTX	MTX, Antiaggregants	15	CDUS, MR angiography	7	4 mg/kg every 6 wks
11	28; 31	26	26	_	GC, MTX, CYC	MTX, Antiaggregants	10	CT/PET, CT angiography, cardiac catheterisation	1	3mg/kg every 4 wks
12	28; 35	23	25	_	GC, MTX, CYC	MTX, Antiaggregants	5	CT angiography, MR angiography, CT/PET	2	4 mg/kg every 4 wks
13	38; 41	34	35	_	GC, MTX, CYC	MTX, Antiaggregants	40	CDUS, brain MR angiography, and conventional angiography	9	3 mg/kg every 6 wks
14	39; 42	36	38	_	GC, MTX, CYC, ADA	MTX, Antiaggregants	12,5	CDUS, CT/PET	4	4 mg/kg every 4 wks
15	16; 25	11	11	Arnold Chiari syndrome; Morquio syndrome	GC, MTX, CYC, AZA	MTX, Antiaggregants	5	CT/PET, MR angiography	3	2 mg/kg every 4 wks

DM: diabetes mellitus; OP: osteoporosis; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids; MTX: methotrexate; CyA: cyclosporine-A; AZA: azathioprine; MMF: mycophenolate mofetil; CYC: cyclophosphamide; ADA: adalimumab; CDUS: colour Doppler ultrasound; MR: magnetic resonance; MRI: magnetic resonance imaging; CT: computed tomography; PET: positron emission tomography; IFX: infliximab; BVAS: Birmingham Vasculitis Activity Score; wks: weeks; F-up: follow-up.

Table II. Clinical outcome at the last follow-up.

Patient	Remission (Y/N)	Time to remission (months)	n° of relapse and time to relapse (months)	Surgical procedure (Y/N)	Adverse events	IFX last dose	Imaging	Prednisone or equivalents (mg/day)	BVAS
1	Y	12	2 (+6;+15)	N	N	7.5 mg/kg every 6 wks	Unchanged	0	5
2	Y	48	3 (+60; +73; +81)	N	N	6 mg/kg every 6 wks	Unchanged	2.5	0
3	Y	6	4 (+13; +42; +54; + 63)	Y	N	5 mg/kg every 7 wks	Unchanged	0	4
4	Y	7	2 (+35)	Y	N	8 mg/kg every 6 wks	Unchanged	0	9
5	Y	13	1 (+37)	N	N	5 mg/kg every 8 wks	Unchanged	0	7
6	Y	10	1 (+27)	N	N	5 mg/kg every 6 wks	Improved	0	4
7	Y	6	1 (after discontinuation)	N	N	4 mg/kg every 5 wks	Unchanged	2.5	0
8	Y	4	1 (after discontinuation)	N	N	4 mg/kg every 5 wks	Worsening*	5	0
9	Y	27	1 (+23)	N	N	4 mg/kg every 5 wks	Improved	5	0
10	N	_	_	N	N	4 mg/kg every 4 wks	Unchanged	15	6
11	N	_	_	N	N	switch to RTX (month +10)	Worsening*	10	0
12	Y	3	_	N	N	IFX discontinuation (month 62+)	Unchanged	1.25	1
13	Y	3	_	N	N	3 mg/kg every 6 wks	Unchanged	5	9
14	N	_	_	Y	Infusion reaction	IFX discontinuation (month +3)	Not done	10	3
15	N	_	_	N	N	switch to ETN (month +4)	Not done	5	3

Y: yes; N: no; IFX: infliximab; RTX: rituximab; ETN: etanercept; BVAS: Birmingham Vasculitis Activity Score.
*appearance of new stenoses observed with CDUS (patient n. 8); increased vascular CT/PET FDG uptake and progression of stenoses observed with cardiac MRI and echocardiography (patient n. 11).

the initiation of infliximab (Table I). Response to infliximab was evaluated according to the physician in charge of the patient, and separately by the presence of clinical disease and of biological activities.

Evaluation of SF-36 questionnaires was made at baseline at the last follow-up in patients continuing infliximab at the last follow-up. HRQOL was evaluated with the SF-36 Health Survey, a generic self-reported health questionnaire administered in the patient's native language. The SF-36 measures HRQOL in 8 domains, 4 physical [physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH)] and 4 mental [social functioning (SF), role emotional (RE), mental health (MH), and vitality (VT)]. The score for each domain was normalised to Italian population scores with a mean±SD of 50±10, with higher scores indicating better quality of life (18). In addition, domains are summarised as a physical composite summary (PCS) and a mental composite summary (MCS), also with a US normal population with mean±SD of 50±10, in order to compare the present cohort with US cohorts of TA and ANCA-associated vasculitis (AAV) (19, 20). A 5-point difference in scores is generally regarded as the minimum clinically important difference (MCID) for PCS and MCS (21). SF-36 summary scores were compared with those of TA patients published in literature (3).

EQ5D scores were also calculated from SF-36 questionnaire results, by using a published algorithm (22).

One-sample *t*-test was used to compare norm-based PCS and MCS values from our series with those of other series with TA patients and those of AAV series (for comparison with small vessel vasculitis).

Paired sample test or Wilcoxon signed rank test was performed to compare PCS, MCS and EQ5D scores at baseline with the respective values at the last follow-up, after verifying the assumption. Parametric or non-parametric correlation analyses were used to explore the possible associations between PCS, MCS and EQ5D and baseline BVAS. All statistical tests were two-sided and a $p<0.05$ was considered to be statistically significant. The results are expressed as mean and standard error of the mean.

This study was approved by the Institutional Review Boards of University of Udine, Padova and Pisa.

Results

Clinical efficacy

The outcomes [remission (y/n) and time to remission] at the last follow-up, number of relapses and time to relapse, infliximab dose variation during follow-up, steroid dose at the last follow-up, and side effects are described in Table II.

All but one patient were treated with infliximab after inefficacy of high doses of glucocorticoids alone (1/14) or in combination with several immunosuppressors (13/14), including methotrexate (13/15), cyclosporine-A (2/15), azathioprine (3/15), mycophenolate mofetil (1/15), cyclophosphamide (6/15) and adalimumab (2/15) (Table I). In the remaining patient, infliximab was used as first-line therapy. Methotrexate 7.5-15 mg/week was concomitantly administered in 14/15 patients, while high doses of glucocorticoids in 5/15 (Table I). Mean follow-up after initiation of infliximab was 74±44 months (range 10–162). Median time from diagnosis to infliximab initiation was 12 months (range 0–96 months). Infliximab was still ongoing at the last follow-up in 11/15 patients. Overall remission at the last follow-up was noted in 11 (73.3%) of the 15 cases, and infliximab was discontinued for stable remission in 1

out of 11 patients at the last follow-up. Absence of clinical response was noted in 3/15 (20%), while infliximab was stopped for infusion reaction in the remaining patient. Thirteen relapses under infliximab occurred in 7/11 (63.6%) patients during the follow-up; 8 out of 13 relapses (61.5%) occurred just after infliximab dose/interval reduction. Three out of seven patients showed further relapses after infliximab dose or interval adjustment; thus, the overall rate of relapses after infliximab dose/interval adjustment decreases to 3/11 (27%). First relapse occurred after a mean time of 27±18 months. Two other relapses occurred after infliximab suspension due to stable remission or pregnancy. Infliximab dose increase (up to 10 mg/kg every 6 weeks) and/or reduction in the interval between infliximab infusions were effective to re-established remission in 7/7 patients. Reinstitution of infliximab with a new induction course was effective in the other two patients, who did not complain of any relapse in the subsequent follow-up.

Significant reduction in BVAS score was noted at the last follow-up [from 4.0 (1–16) to 3.0 (0–9), p=0.003].

Significant steroid dose reduction was also recorded [from 10 mg/day (0–50) to 2.5 mg/day (0–15), p=0.005)], and steroid suspension occurred in 5/11 responder patients.

At the last follow-up, normalisation of CRP or ESR was noted in 8/12 (66.7%) and in 9/15 (60%) patients with increased values soon before infliximab therapy, respectively; platelet count was normalised in 5/7 (71.4%) patients with increased values soon before infliximab therapy; finally, haemoglobin levels and total leukocyte value were normalised in 2/10 (20%) and in 1/2 (50%) patients with abnormal values soon before infliximab therapy, respectively.

Radiological disease activity was assessed in 13/15 during infliximab therapy, with evidence of improvement in 2/13, stable disease activity in 9/13, and worsening in 2/13 (Table II).

Three patients (20%) underwent surgical procedure during the follow-up.

Quality of life evaluation

Many aspects of HRQOL in patients with TA were impaired, with major involvement of physical domains (BP and GH, in particular) (Table III). PCS and MCS were as impaired as observed in patients with TA from the largest published cohort (Table IV). However, AAV showed higher impairment of PCS than that observed in TA (Table IV), while MCS did not show any difference between TA and AAV (Table IV).

No correlation was seen at baseline between BVAS and PCS (p=0.2), BVAS and MCS (p=0.7), and BVAS and EQ5D (p=0.5).

Infliximab significantly improved BP (40.0±32.3 *vs*. 67.2±27.6, p=0.035), and GH (31.2±21.5 *vs*. 54.9±21.1, p=0.007) among physical domains, and VT (47.0±28.7 *vs*. 67.0±20.3, p=0.01) among mental domains of SF-36 (Table V). Also, all the other physical and mental domains showed improvement, though not significant (Table V). Overall, infliximab significantly improved PCS (36.2±10.9 *vs*. 44.3±7.0, p=0.015), also MCS improved even if not significantly (40.0±15.0 *vs*. 47.7±14.0, p=0.1). In addition, infliximab significantly increased EQ5D (0.57±0.2 *vs*. 0.73±0.2, p=0.048).

At the last follow-up, BVAS did not correlate with PCS (p=0.1), or MCS (p=0.9), or EQ5D (p=0.3) at the same time evaluation.

Finally, the time interval from diagnosis and infliximab initiation did not

Table III. SF-36 domains in TA and comparison with norm-based Italian population.

Domain	Mean raw score (SEM) n=10	Mean raw score (SEM) n=2031 (ref. 18)	Mean Z-score
PF	64.5 (10.2)	84.5 (0.01)	-0.9
RP	37.5 (13.0)	78.2 (0.02)	-1.3
BP	40.0 (10.2)	73.7 (0.01)	-1.5
GH	31.2 (6.8)	65.2 (0.01)	-2.0
VT	47.0 (9.1)	61.9 (0.01)	-0.7
SF	49.9 (9.7)	77.4 (0.01)	-1.5
RE	43.2 (12.2)	76.2 (0.02)	-1.1
MH	57.3 (8.7)	66.6 (0.01)	-1.0

PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; SF: social functioning; RE: role emotional; MH: mental health; VT: vitality; SEM: standard error of the mean.

Table IV. Physical and mental composite scores in TA and comparison with TA cohort and ANCA-associated vasculitis cohort published in literature.

Disease	n.	PCS (SEM)	MCS (SEM)
TA (present series)	10	36.2 (3.4)	40.0 (4.7)
TA (ref. 3)	158	39.2 (1.0)	44.5 (1.0)
AAV (ref. 20)	346	27.6 (0.7)*	40.4 (0.6)

*p<0.05. PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; SF: social functioning; RE: role emotional; MH: mental health; VT: vitality; SEM: standard error of the mean; PCS: physical component summary; MCS: mental component summary; TA: Takayasu's arteritis; AAV: ANCA-associated vasculitis.

Table V. SF-36 domains in the course of Takayasu's arteritis in 10 patients under infliximab.

Domains	Baseline	Last follow-up	p-value
PF	64.5 ±32.6	71 ± 30.2	0.282
RP	37.5 ±41.2	65 ± 33.7	0.111
BP	40 ±32.3	67.2 ± 27.6	0.035
GH	31.2 ±21.5	54.9 ± 21.1	0.007
VT	47 ±28.7	67 ± 20.3	0.01
SF	49.9 ±30.6	68.6 ± 26.5	0.17
RE	43.2 ±38.6	59.9 ± 43.9	0.296
MH	57.3 ±27.5	72 ± 25.6	0.056

PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; SF social functioning; RE: role emotional; MH: mental health; VT: vitality. Values are reported as mean±standard deviation.

influence the degree of improvement in BVAS, PCS, MCS, or EQ5D scores (data not shown).

Tolerability

No relevant side effects or severe infections were recorded during the whole follow-up under infliximab. One patient suspended infliximab due to infusion reaction.

Discussion

TA is a giant cell, immune vasculitis causing inflammation of the aorta, its major branches, and the pulmonary arteries (1). Since 2004, anti-TNF therapy has been proved effective in relapsing TA (8), and this first clinical observation was supported by subsequent observational studies and case series (9-13), and by *in vitro* studies (7).

This study further supports the usefulness of infliximab in TA, highlighting both the efficacy and the safety in a very long-term follow-up, and in very refractory cases. In addition, steroid sparing effect of this therapy was also supported. The quite heterogeneous infliximab starting doses and subsequent management reflect both the retrospective nature of this study performed in three Italian reference centres for the cure of the rheumatic diseases, and the absence of guidelines in refractory TA (23). Besides this limitation, our study supports some clinical information coming from previous larger studies and can add new insights in the management of TA with infliximab in particular, exploring also the effect of this drug on the HRQOL in TA in a long-term follow-up.

The efficacy of dose adjustment of infliximab or a new course of induction with infliximab at the time of relapse, might suggest that a new induction of remission may be obtained with higher serum concentration of anti-TNF rather than switching to a different biologic agent. Notably, a lower rate of remission and a greater rate of relapse were observed in our study, if compared with previous ones (8-13); the longer follow-up time may explain this difference. However, only about one-third of the patients relapsed after infliximab dose adjustment, and two thirds of the relapses occurred during attempt at drug reduction. Finally, an infliximab dose ≥5 mg/kg might be necessary for TA, since the majority of patients required higher doses as maintenance than those administered in the induction phase, in our experience. Randomised controlled trials of infliximab in TA should answer the questions about the efficacy of infliximab in TA and the best dose/interval of administration.

Only three surgical procedures were recorded in our cohort, unlike the rate reported by other studies in which a vascular procedure was required in about 50–60% of patients (24-26). Early administration of infliximab may be linked to a favourable outcome in the long term, since a median delay of only 1 year was observed in our patients from TA diagnosis to infliximab administration. Radiological improvement was seen only in 2/13 patients, but a correlation between disease activity, as measured by BVAS, and radiological changes was not observed in our study. Also, only 33% of patients in remission showed a BVAS score of 0 at the last follow-up. However, the best imaging study to monitor disease activity in patients with TA is an open debate at the moment. Persistent disease activity in TA may remain subclinical for a long time, as occurs in rheumatoid arthritis (27); in fact, Kerr's National Institute of Health criteria for TA showed a limited sensitivity, since more than 50% of patients with "inactive" disease according to these criteria had progression of angiographic lesions, and 44% of patients had histologically active disease on surgical bypass biopsy specimens (1).

To our knowledge, this study represents the first evaluation of the quality of life of patients with TA under infliximab therapy, by using a validated health related HRQOL questionnaire.

Baseline PCS and MCS scores were not different from the scores reported in the largest series (3), physical domains being more affected by the disease. Baseline MCS in TA was also not different from MCS score in AAV, which affects small vessels, while PCS score was less affected in TA (20). Since chronic peripheral neuropathy significantly lowers HRQOL in AAV, while it is generally absent in TA, physical domains in AAV patients may be more affected. Notably, infliximab improved those physical domains showing the worse scores at baseline (*i.e.* BP and GH), and also VT score, thus determining a significant improvement in the PCS, and also an improvement over the MCID in the MCS scores. Since an inferior physical HRQOL was encountered in a previous study in patients who were older and on immunomodulating medications (3), the steroid sparing effect herein remarked may be also implicated in the improvement in HRQOL. The absence of correlation of HRQOL with BVAS further supports the notion HRQOL cannot be reduced to biological effects of the disease and that accounting for many other factors is important, as observed in other vasculitides (20, 28). Notably, the lack of correlation between BVAS and HRQOL measures might also be related, at least in part, to poor construct validity of the BVAS for large-vessel vasculitis (16).

In conclusion, infliximab showed a sustained clinical improvement in the long-term in TA, with significant benefits on quality of life. Early administration of infliximab may be encouraged in this disease. Controlled trials with long term follow-up and HRQOL evaluation are required (23, 29).

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