Update on Takayasu's arteritis

Dott. Giuseppe Germanò
REUMATOLOGIA
Arcispedale S.Maria Nuova
Reggio Emilia
Takayasu's arteritis

Mikito Takayasu, a professor of ophthalmology at Kanazawa University, Japan, first described Takayasu's arteritis (TAK) as a case of retinal vasculitis with pulselessness in 1908.
General aspects
- Genetics
- Classification
- Prevalence and ethnicity
- Clinical course
- Prognosis
- Assessment of disease activity
- Imaging in TAK
- Biomarkers
- Damage assessment and patient reported outcomes
- Treatment
- Conclusion
TAK is a chronic, *large-vessel vasculitis* (LVV) with a granulomatous histology, occurring *predominantly in females in the second or third decades of life*.
Most frequently involved large arteries are ascending/descending aorta, subclavian and extra-cranial arteries such as carotids (60–90%).
• The disease is observed worldwide
• Genetic factors associated with ethnicity
• Most of the patients were reported from **East Asian countries** (Japan, India, Korea and also recently from Middle-East, especially Turkey)
• **Indolent early course** with constitutional features (fever, malaise, anorexia and weight-loss), extremity pain/claudication and light-headedness.
• Absent or diminished pulses, loss of blood pressure and bruits are characteristic and present according to the vessel involvement
Although prognosis is improved, there is still a significant delay in the diagnosis and mortality is increased, with a high rate of new, severe manifestations after diagnosis.
Genetics
Classification
Prevalence and ethnicity
Clinical course
Prognosis
Assessment of disease activity
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
Genetics

- HLA-B52, and to a lesser extent B*67 in Japan, as the most important HLA alleles associated with TAK in different ethnicities.

- HLA-B51 and B52, have only two amino acid differences in antigen-binding groove, they are associated with completely different diseases: B*51 with Behcet's disease (an autoinflammatory disorder), B*52 with TAK (a granulomatous nature)

Genetics

**Classification**

Prevalence and ethnicity

Clinical course

Prognosis

Assessment of disease activity

Imaging in TAK

Biomarkers

Damage assessment and patient reported outcomes

Treatment

Conclusion
Usefulness of this criteria may be limited in real-life setting to differentiate TAK from giant-cell arteritis (GCA), atherosclerosis, congenital aortic vessel disease and the new entity IgG4-related disease.
Genetics
Classification
Prevalence and ethnicity
Clinical course
Prognosis
Assessment of disease activity
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
Prevalence and ethnicity

• The incidence is 1-3 new cases per year per million population in the United States and Europe
• Prevalence is thought to be >0.004%
women 87.5% and men 12.5%  
Mean age at disease onset was **29.2 years**

Looking at all the possible combinations of 3 diagnostic criteria, the most frequently observed combination was:

- decreased brachial artery pulse
- blood pressure difference > 10 mm Hg
- and typical arteriogram abnormalities (61% of cases).

Median diagnostic delay was 15.5 months (range 0 –325 months). Only 2 variables as predictors of diagnostic delay:

- **age at onset** 15 years, which was associated with a higher probability of a delay ≥2 years
- **ESR at onset** >30 mm/h, which was associated with a lower probability of delay
Clinical course
Clinical course

- Among different vasculitides, TAK has the highest rate of new severe manifestation (ischemic, vascular) incidence (44%)
Clinical course

• “vascular symmetry” in TAK

• A similar observation is also present for GCA
Clinical course

- at the onset, 70.9% of the patients had at least one constitutional or musculoskeletal symptom.

- Stenosis was the most frequent lesion, being present in 93%. Occlusion 57%, dilatation 16%, and aneurysm 7%.

- Stenosis was present in 19% of all the examined vessels, occlusion 7%, dilatation 1%, aneurysm 0.5%.
The majority of the patients (53%) had lesions above and below the diaphragm.

32% isolated supradiaphragmatic disease

Involvement of the abdominal aorta and its branches alone was rarely documented (7%)
In 44% of the patients, the subclavian or axillary arteries of both arms were either stenotic or occluded.
Takayasu’s Arteritis: A Study of 104 Italian Patients

M. Vanoli, E. Daina, C. Salvarani, M. G. Sabbadini, G. Rossi, G. Bacchiani, G. Schieppati, E. Baldissera, G. Bertolini, and the ITACA STUDY GROUP

Clinical course

- aneurysm became evident after at least 3 years of disease
- the number of lesions per patient increased with disease duration
- No significant correlation between hypertension and presence of dilatation or aneurysm was found.
Clinical course

- Hypertension
- Aortic regurgitation
- Valvular disease
- Ischemic heart disease
- Coronary stenosis and occlusion
- Stenotic lesions and occlusion of pulmonary arteries were detected
- Hypertensive retinopathy
- Ischemic retinopathy
- Stroke
Pregnancies complications:

- Hypertension
- Preeclampsia
- Postpartum hemorrhage
- Preterm labor
- Intrauterine growth restriction
- Neonates requiring NICU admissions.
- Abortions
Prognosis
Prognosis

- Mayo Clinic long-follow-up: **overall survival was 97% at 10 and 86% at 15 years**

- Mortality was still increased compared to the general population (SMR: 3.0).

- Disease **phenotype and severity may give rise to different mortality rates**.

Prognosis

- **Arterial reconstruction and bypass grafting** may be necessary in up to 70% of patients (for example renovascular hypertension).

- **The restenosis rate** after bypass procedures = 5–31%.

- **Percutaneous transluminal angioplasty/stenting** has a higher restenosis rate (12-71.4%).

- The restenosis rate was reduced when surgical treatment was performed **during the inactive stage of the disease** and under treatment with **both glucocorticoids and immunosuppressive (IS) agents**.

- **Early immunosuppression** and the choice of treatment might be influencing the different rates of outcome in the literature.

Assessment of disease activity
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
The most commonly adopted approach for disease assessment in TAK is the simple definition of "active disease":

- constitutional symptoms
- new-bruits
- elevated APRs
- new angiographic features.

Imaging in TAK
Imaging in TAK has relied on conventional angiography, which demonstrates mainly luminal blockage rather than vessel wall involvement.
Computerized tomography (CT) provides excellent anatomical characterization of structural aortic changes, but is limited in its assessment of early disease activity.

MR angiography

- MR angiography can show vessel wall thickening and edema, however this correlates poorly with clinical activity or APR and is shown to have a limited role for long-term follow-up.

18-FDG-PET

• 18-FDG-PET is the most sensitive test for early vessel inflammation, however, it requires CT or MR imaging for anatomic localization.

• Activity in 18-FDG-PET is suggested to demonstrate active or relapsing disease.

Imaging in TAK

PET

- Before Therapy
- After
Ultrasonography

- Ultrasonography (US) has the advantages of avoiding the high radiation dosage of angiography or 18-FDG-PET, and is cheaper and more widely available.
Wall swelling

- Homogeneous
- Symmetric
Genetics
Classification
Prevalence and ethnicity
Clinical course
Prognosis
Assessment of disease activity with new outcome tools
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
Acute-phase response (ESR and C-reactive protein) is frequently advocated for disease assessment in TAK.

Serum autoantibodies (anti-endothelial antibodies, and serum biomarkers such as VEGF, IL-6, IL-8, IL-18, matrix metalloproteinase-9 and adipokines) are also investigated.
Recently **Pentraxin3** (PTX3), which is produced by immune and vascular cells in response to proinflammatory signals, is suggested as a biomarker for disease activity in patients with TAK
Biomarkers

In a single center study from Italy, levels of PTX3 were higher in patients with active TAK (median > 2.14 ng/mL) than in inactives (0.63 ng/mL), patients with infections (0.26 ng/mL) and healthy controls (0.11 ng/mL).

In another study from Japan, among 28 patients with active TAK, 71% was positive for CRP and 82% for PTX3.

However, these data require confirmatory studies to show whether PTX3 is superior to CRP.

Genetics
Classification
Prevalence and ethnicity
Clinical course
Prognosis
Assessment of disease activity with new outcome tools
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
Why management of TA is not easy?
Treatment

- First, early diagnosis is difficult and requires clinical awareness and suspicion
- Second, and even more important, is the lack of standard and reliable parameters reflecting disease activity
- Systemic inflammatory response does not always show a positive correlation with inflammatory activity in the vessel wall.

Why management of TA is not easy?
TA may be active despite a normal ESR and serum CRP level, and vice versa.

In patients with apparent clinical and laboratory remission, arterial specimens may show histological signs of vasculitis.

Why management of TA is not easy?
Corticosteroids

- In the presence of active disease, standard initial treatment of TA is high-dose (1 mg/kg/day) prednisolone or its equivalents.
- The response to high-dose prednisolone is generally favourable, but relapses may occur while gradually tapering the dose and adverse effects of long-term treatment can cause problems.
TERAPIA STEROIDEA NELLA AT

- si inizia con 50 mg die di prednisone
- dopo un mese si riduce il prednisone se: 1) tutti i sintomi di arterite sono scomparsi, 2) normalità della VES e PCR.
- la velocità di riduzione è di 6,25 mg di prednisone alla settimana sino alla dose di 37,5 mg/dì, poi di 2,5 mg la settimana sino alla dose di 25 mg/dì, e quindi di 2,5 mg ogni due settimane sino alla dose di 10 mg al dì.
- Al di sotto dei 10 mg/dì riduciamo di 1 mg ogni due settimane
IS conventional-TNFaa-TCZ-RTX

- Major limitation for randomized controlled trials (RCT).
- There are no RCTs published in TAK.

- Treatment choices are mainly determined by observational studies and the clinicians’ decision based on expert opinion.

- in EULAR guidelines for the management, where, except IS use, all recommendations have an evidence level of 3 and strength of C.
Conventional IS agents

- MTX is an inexpensive, easily available and relatively safe agent that is widely used in rheumatology, it is the first choice of many physicians.
- The data regarding MTX use in TA is limited and generally is in the form of case reports and few small open studies.
- Hoffman et al. reported 16 patients with TA given standard CS treatment plus MTX (mean dose 17 mg/w): 13 patients (81%) went into remission and 8 patients (50%) remained in remission for a mean period of 18 months.

• AZA is another IS agent widely used for the treatment of TA.
• Besides case reports, there is only one open study from India 2 mg/kg/day for 1 year, in a series of 15 patients.
• AZA in addition to CS treatment (Prednisolone: 1mg/kg/day for 6 weeks, followed by taper to 5 to 10 mg/day within 12 week): Acute phase responses were significantly reduced, no adverse events occurred and control angiography showed no progression.
• However, long-term follow-up of these patients was not reported
CYP:
Most of the case reports with CYP use in TA include severe cases with at least one of the following conditions: retinal vasculitis, pulmonary artery involvement with or without aneurysm, severe aortic regurgitation or myocarditis.
• MMF, is also a promising agent in TA. In a observational study of 21 TA pts, followed for 9.6 months, 11 on steroid alone, 10 have received AZA prior to MMF .
• 19 pts were in active disease. 1pt Drop out.
• 20 pts: improvement in disease activity, with significant decrease in steroid dosage, from 36 mg/day(+- 16 mg) to 19 (+-14) at last follow-up (p<0.001)
Treatment

• CSA, tacrolimus and LEF were also tried in selected cases with successful results
Refractory disease in TA

• refractory disease was accepted if disease activity increased following reduction of the CS dose or persisted despite use of at least one conventional IS agent.

• refractory disease: angiographic or clinical progression despite treatment or the presence of any of the following characteristics:
  1. prednisolone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents
  2. new surgery due to persistent disease activity
  3. frequent attacks (more than three per year)
  4. death associated with disease activity.

Biologic agents

- infliximab (IFX), were tried in refractory TA patients. There are many case reports and series showing beneficial effects in both adult and pediatric patients.


Treatment

RTX

• Good clinical response to rituximab, evidenced by improvement in clinical signs and symptoms, in patients with refractory TAK despite prednisone, IS, and TNFα Blockers.


Hoyer BF, Mumtaz IM, Loddenkemper K et al. Takayasu arteritis is characterized by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. Ann Rheum Dis 2012;71:759.
Since IL-6 is highly expressed within inflamed arteries and serum levels correlate with disease activity, blocking IL-6 may be effective in TA.

First report of successful use of tocilizumab in a patient with refractory TA was published in 2008.

In the majority of the cases, disease activity improved and CS doses were discontinued or tapered.


Genetics
Classification
Prevalence and ethnicity
Clinical course
Prognosis
Assessment of disease activity with new outcome tools
Imaging in TAK
Biomarkers
Damage assessment and patient reported outcomes
Treatment
Conclusion
TAKE HOME MESSAGE

• Assessing disease activity is essential for tailoring treatment in Takayasu arteritis.

• Biologics should be tried in treatment-resistant Takayasu arteritis patients.

• Revascularization procedures may be performed during the inactive phase of Takayasu arteritis.