

# Our Experience with The Use of Interleukin 6 Inhibitor - Tocilizumab, In the Complex Treatment of Nonspecific Aortoarteritis

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**Abstract:** The need for further improvement of treatments for Takayasu's arteritis (TA), the progress in understanding the mechanisms of the disease, and the introduction of biological agents (BA) in rheumatology practice have created preconditions for developing a new TA pharmacotherapy using BA associated with interleukin 6 (IL-6) inhibition.

The authors describe their two own cases of tocilizumab (TCZ) use for complicated TA. In one case with a long history of complicated TA and glucocorticosteroid intolerance, the use of TCZ contributed to the control of disease activity. In the other case with the onset of TA and focal pulmonary tuberculosis (TB) treated with anti-TB drugs during TCZ monotherapy for 6 months could control TA and achieve TB cure.

The use of IL-6 inhibitors should be considered as a potentially effective and relatively safe innovative (off-label) treatment for refractory TA in patients with intolerance or contraindications to standard therapy, which requires further larger randomized clinical trials.

**Keywords:** Nonspecific aortoarteritis ; Takayasu's arteritis; interleukin 6; tocilizumab.

**Introduction:** Takayasu arteritis ( TA ) or nonspecific aortoarteritis is systemic in the group of vasculitis ( TV ) . disease big, big of the veins damage with is described, usually from the age of 50 small in patients develops and a medium and his/her main networks Arteritis, often granulomatous, superior contamination with is described. [1].

The etiology of TA is unknown, the influence of genetic factors is more discussed, and TA is considered a typical

HLA class II disease, in contrast to giant cell arteritis (GCA), another form of large-vessel TB that is associated with HLA class I. [2-4]. Antibodies have been shown to be associated with HLA-Bw52 and HLA-B39 [3, 5], and patients with the HLA-B39 allele have been shown to respond poorly to standard immunosuppressive therapy and require the use of GABA (genetically engineered biological drugs) [6].

The rarity of TA, the variability of the lesion sites [7],

and the lack of standard reliable instrumental or laboratory markers of activity [8] explain the lack of randomized controlled trials on TA until recently. According to the results of retrospective observational studies, standard treatment with glucocorticoids (GCs) and cytostatics, primarily methotrexate (MT) [9] may not be sufficient to achieve complete stable remission of TA. Thus, D. Freitas et al. [10] During treatment with GCs and MT, the progression of the disease is detected in 75% of cases with new localization of vascular damage during instrumental examination. According to various authors, relapses develop in 22-72% of patients with TA with a decrease in the dose of GCs [11-13]. In turn, the complications of GCS therapy can compete with the complications of the underlying disease. In addition, the use of GCS in patients with renal artery disease is limited due to the increased risk of secondary hypertension.

In patients with clinically hemodynamically significant circulatory disorders, surgical treatment is used, i.e., angioplasty or stenting is used for high-grade arterial stenosis; in stenosis accompanied by severe periarterial fibrosis or occlusive stenosis, bypass and other reconstructive procedures are performed. Surgical procedures are never performed in the active phase of TA. However, during routine examinations, the activity of the disease may not be evident, segmental inflammation of the blood vessel wall sometimes proceeds subclinically, and laboratory tests do not correspond to the activity of inflammation, which can lead to ineffective surgical treatment. Thus, as reported by K. Maksimowicz-McKinnon et al. [13], despite the initial successful results of vascular surgery, subsequent re-stenosis developed in 78% of cases of angioplasty and in 36% of patients after bypass/reconstructive intervention. According to the results of the observations of M. Isobe et al. [14], 3-6 years after bypass surgery, occlusion or restenosis is observed in 8-31% of patients with TA.

In recent years, the need to further improve the treatment of TA, advances in understanding the basic mechanisms of TA pathogenesis, and the introduction of genetically engineered biological drugs ( GEBDs ) into rheumatology have created the necessary conditions for the development of a new direction in recent years. GEBDs with the help of TA 's pharmacotherapy, first in turn, is associated with inhibition of interleukin 6 (IL-6). Treatment of T A potential target for as IL- 6 importance Suffering from TA aorta in patients and large veins of IL-6 in tissues exactly expression [15, 16] and IL - 6 and his/her soluble receptors in serum concentration [16-21], in serum soluble IL-6 receptors level and TA activity [21 ] . Interestingly is that it is different from TA as, activity in Γ C A his/her soluble not

related to receptors, but to IL-6 was.

Since 2008 [22], tocilizumab (T Ts Z), IgG 1 immunoglobulin lower from class human IL-6 receptor for recombinant humanized monoclonal antibodies, soluble and selectively with membrane IL-6 receptors binds, suppresses classical and trans-signaling IL. 6 receptor pathways 6 individual cases of TA, especially to standard therapy durable or to him against to the instructions owner those who were in treatment successful is used. Recently small Japanese couple randomized, placebo- controlled, phase III test (RP C T) first The results are presented in [23]. They are refractory TA remission save stay for T Ts Z security and efficiency studied.

## METHODS

We are G K C and from cytostatics limited complicated to use Using T Ts Z in TA according to two own our observations present We will.

Patient M. From the age of 13, repeated erythema nodules and arthralgias appearance sick since. from 2017 from up to 39°C fever added, blood pressure (AQB ) 200/100 mm .sim .ust. rose to B soup pain , up to 7 times a day unconscious to leave , to leave of the hand inactivity was observed . 2017 in September of the year first pregnancy during inspection on time Doppler to ultrasound ( ultrasound ) data according to general sleep artery stenosis is determined up to 70% . Pregnancy medical for reasons according to stopped .

In December 2019 when checked C - reactive protein ( CRO ) level is 34 mg/l, hypercoagulation signs , selective in angiography left general sleep artery ( IUA ) up to 70% stenosis, external U A has up to 80% stenosis approved . TA diagnosis placed of India blood vein surgery in the department left general UA alloprosthesis to do increased , surgery from treatment then situation noticeable to the extent improved , but left in hand weakness and insomnia preserved left .

2021 January in the month second pregnancy during , 6 weeks for the period . left inner and outside In the UAE blood of the stream with preservation of the total UA prosthesis occlusion diagnosis was put of the situation progressive deterioration, unconsciousness leave, dizziness, left hand of your fingers movement weakening, unstable blood pressure 210/100 mm. raised to Pregnancy during Clexane 40 mg per day was made. From March 2021 from Republican surgery angioneurology specialized in the center treatment started and observed.

36 weeks in September 2021 during pregnancy cesarean section Successfully cut the road with a dead end the birth was done. Originally from Russia later arteriodynia record was made , colored Doppler

ultrasound to check according to the left inner U of A stenosis added up to 50% . Belly space aorta and his/her on the horns injury signs no . Methylprednisolone 20 mg per day subjective tolerance , blood pressure increase ordered with episodes . One- time from injection then MT 10 mg of transaminase levels increase because of useless done , heart nausea , diarrhea and Azathioprine (AZA) 100 mg daily was prescribed , treatment was further complicated by dyspepsia. complicated . Clexane - 60 mg per day . To treatment despite ultrasound during the inspection left internal U A stenosis increased to 80% and left outside The wall of A thickening added .

20 22 - in March T Ts Z 8 mg/ kg first and second injections with an interval between 2 weeks , then 4 weeks , the last infusion 20 22 years October in the month added . T C Z is one with monthly from treatment then C R O level is 1.7 mg /kg did E ChT - 11 mm/ h , thrombocytes -  $321 \times 109/l$ .

20 in November 22 In India to the patient left internal and on the side outside U A main in blood current restored in case subclavian-general sleep prosthetics successful was conducted . From the operation next early during complications not observed , CRO - 16 mg/l, thrombocytes -  $423 \times 109 /l$ , procalcitonin test is negative .

202 3 - year February in the month planned inspection at the time : C P O level - 0.9 mg/l, ESR - 14 mm/ h , platelets -  $420 \times 109/l$ , colored Doppler ultrasound during the inspection blood vein prosthesis you can see that the blood flow is good .

TA of far continue which natural course ( immunosuppressive 15 years without therapy ) under observation to other localization arteries damage non-transmission , improvement of turgor , treatment with T C Z during C R O level normalization inflammation effective evidence of reduction gives .

**Second sick woman patient M.,** 20 years old , April 2018 month from a respiratory infection then cough , in May 2018, the Republican Phthisiology and pulmonology in the center passed inspection on time right lung high part of focal tuberculosis determined . diagnosis placed and treatment with pyrazinamide , rifampicin and ethambutol ordered . Soon general weakness , fever up to  $38^{\circ}\text{C}$  , high on the feet pain , headache , fainting once departure is added . Right on the side blood pressure when checking - 100/70 mm .sim .ust., left - 70/40 mm .sim .ust. , C R O level - 21.2 mg/l, Doppler ultrasound - general It's A 's. two side by side stenosis up to 60-85%, subspinal arteries - up to 65-80%. July 2018 from the month Since the Republic is specialized surgery angioneurology in the center is being observed . TA diagnosis Joint work with

phthisiologists from consultation then , GK C from of use sharp limitation and potentially more convenient due to security profile , 2019 February 8 mg/kg T C Z was added at 4 -week intervals until the end of the month , for a total of 3 infusions . Treatment as a result the rise in body temperature is gone , in the hands of pain noticeable to the extent decrease , unconsciousness of leaving absence and C R O level positive with normalization impact record was done .

From September 2019 from 7 months then T C Z 's last from infusion then , general weakness , fever up to  $38^{\circ}\text{C}$  , myalgia , shortness of breath heart rate palpitations , headache in the form of of health progressive deterioration . When examined in computed tomography (CT) , right your lungs high in the future pleuroapical contracts and local fibrosis had the appearance , negative Mantoux test , tuberculosis treatment It will be shown .

Again during examination : C R O - 3 1 , 4 mg/ml, E ChT - 41 mm/s, platelets -  $413 \times 109/l$ , duplex ultrasound also TA in the inspection development signs (Table 1) of blood flow in the brachiocephalic arteries trunk , internal stenosis with the development of . Right side view U A, general U A, right subvertebral artery stenosis development , abdomen aorta of the walls thickening and his/her main visceral branches without signs of stenosis . of stenosis increase and new of injuries appearance with the possibility of of recurrence diagnosis placed .

TA induction Treatment: 4 -weekly intervals with a total dose of 8 mg/kg , 2 infusions in total , Clexane 40 mg/day, then in combination with clopidogrel 75 mg/day positive continue with the effect . With improved stability and mild positive dynamics after 4 months. According to Doppler ultrasound examination of the brachiocephalic arteries (see Table 1). In May 2020, during outpatient follow-up with diffusion-weighted magnetic resonance imaging (DWIMS MRI), evidence of the absence of active inflammation in the walls of the UA on both sides, the main blood flow in the brachiocephalic arteries , bilateral subclavian arteries was obtained. and no changes were observed in all parts of the thoracic aorta, the abdominal aorta and its branches.

T Ts Z monotherapy ineffective to the effect regardless of its efficiency undoubtedly evidence , one from the side , right the subvertebral artery also changed main blood of the stream preserved it remains , this and body temperature with normalization and improvement of stability will come Q is dead of pain disappearance and unconscious of leaving absence , C R O of decrease and other on the other hand , T Ts Z infusions since it ended many without delay negative

dynamics. of observation e -bite the patient's far in the region related to living What is T C Z? take throw during of antibodies activity about of information absence was T Ts Z therapy in the background GCS and cytostatics exception did in case TA activity control to do lung tuberculosis for treatment possibility gave . So so , this in case therapy general effect positive because calculation It is possible , but it is not possible not .

## DISCUSSION

Presentation done initial information that shows that T Ts Zni in TA induction including in treatment refractor on the course effective to be to the potential have Note that should be refractory TA 's general reception done definition no : Rule as , they are GKS dose from decreasing later disease of activity increase or at least one cytostatic to apply despite of activity continue verb means [2]. Turkish researchers [3] refractory TA for criteria offer did : continue doing for treatment despite angiographic or clinical progression; from 6 months later of prednisolone dose  $>7.5\text{mg/day}$  , from cytostatics to use despite treatment ; TA activity because of new operation; frequent relapses ( from 3 times a year more ); TA activity because of death .

Treat T Ts Z in TA general efficiency high indicators about impression (84.6%) each tenth The patient has G K C. and cytostatics every per second , inclusive refractor Treatment with TA successful stop fact confirms . GK S 's dose reduction or take throw opportunity and T Ts Z monotherapy effectiveness [17, 18, 23] in patients with TA in patients additional prospects opens , their most of them are young women . S. Yes and others by to a large study conducted According to [12], 240 pregnancies were recorded in 96 patients with TA . analysis when done , the disease of pregnancy to the result negative impact to show , TA activity , mainly due to arterial hypertension obstetrics and motherhood complications danger increase record treated with T C Z in women pregnancy of the results publication done in the analysis fetus anomalies of danger increase about no what evidence no and early birth level (31.2%) overall to the population relatively increased was determined [12].

To emphasize this It is necessary to treat with T C Z. as a result of the veins narrowly to stay pathological of the process several years from the chair later both return possible . So By Y. Nakaoka and others . [23] and N. Nishimoto and others . [22] TA situations present They did it , it took 4-5 years. continue did disease from activity after using T Ts Z then , narrowed of the veins to recanalization achieved .

French researchers group by take visited one row In studies , treatment with T C Z [24] three annual relapse-free treatments about the information present , which

exceeded the results of standard immunosuppressive therapy ( 58.7%;  $p = 0.0025$ ) and amounted to 85.7% did Twice in remission phase randomized placebo control underneath tests III ( TPNOS ) [23] Maintenance with T Ts Z therapy background , from 6 months later without recitative viability was 50.6% and compared to the PL group (22.9%). high was , but differences are statistically significant owner not was ( $p = 0.0596$ ).

T randomized placebo control underneath results of trials ( TPNOS ) [23]. discussion when doing , GKS is the same as accepted from the moon later properties of reducing the amount in the blood to account to take necessary , this is in clinical practice does not apply and T Ts Z treatment mode for monotherapy brings closer . Send T Ts Z of the subcutaneous route the effect both discussion to do possible , because initial to research according to this T Ts Z dose decrease like negative impact showed [21]. From this except in Japan passed TPNOS the results discussion in doing , suffering from TA in patients clinical course of the disease , including process spread geography and to the nation looking at changed to stand indifferent leaving will not happen .

Initially in research treatment the results in evaluation we improvement or remission included general efficiency seeing We went out because TA activity assessment methods and in sources report The format was very diverse . From except , treated with T C Z Suffering from TA in patients blood vein of the wall inflammation activity too narrow to the extent assessment is very difficult . Y. Seco and to others According to [15], C R O and E CHT degrees to normalize and treatment with T C Z during TA clinical signs of activity to disappear regardless , two from the situation one of them is MR T angiography results blood vein of inflammation continue verb showed . L. Pulsatelli and to others According to [21], 10 patients with TA were treated with T C Z. six infusion ordered ( 9 of them with refractory course) clinical remission in 70 % of patients achieved , clinical activity index positive dynamics , laboratory markers (E ChT, C R O ) and in 60% of cases , it is instrumental methods decreased done .

TA diagnosis put , damage of localization determination and activity observation instrumental studies for value excessive assessment difficult , but this methods always reliable not [8]. Invasive x-ray contrast angiography yet both TA diagnostics for to be the gold standard regardless of its disadvantages there is also , for example , the effect of radiation and contrast material use necessity and them regularly inspection for using will not happen .

So so the initial clinical trials collected information , own our experience and two stage TPNOS III associated with IL -6 inhibitors was Innovative induction of TA and



keeper of treatment It shows the effect and bigger additional randomized clinical trials explanation demand does . The present in time of veins in TA condition about complete information universal representation that gives method exists absence due to , individual methods known and additional for the price Treatment with HAART in the background TA activity monitoring , clinical data , laboratory signs and instrumental vision methods , first first , invasive those who are not every side by side to evaluate to include need .

## CONCLUSIONS

The effect is inhibition of IL-6 to do directed Using GAYaBP A potentially effective treatment for TA and relatively safe innovative ( from label except ) method as seeing discharge need , first in line refractory course, GK and to cytostatics relatively intransigence if , else side to GAYaBPs or standard therapy against instructions existence .

Initially of research collected to the information according to , treatment with T C Z as a result Suffering from TA in 85 % of patients , including refractor remission or improvement observed . I kki side by side TPNOS III According to the phase effect , 6 months with T C Z from treatment later relapse-free period to the PL group than high ( suitable 51 and 23% respectively ), however differences are statistically significant owner not ( $p = 0.0596$ ).

Further clinical studies standardization for Treatment of TA efficiency assessment methods improvement necessary , at the same time GAYAPP treatment with in the background TA activity monitoring , clinical data , modern laboratory biomarkers and instrumental imaging methods , first mainly non -invasive , non-invasive those who were every side by side to evaluate to include need .

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