CHU de Poitiers Hôpital de la Milétrie

GROUPE HOSPITALIER DE LA ROCHELLE - RÉ - AUNIS

Clinical research protocol in routine care

VALIDATION OF A DIAGNOSTIC ALGORITHM FOR GIANT CELL ARTERITIS BASED ON COLOR DOPPLER ULTRASOUND OF THE SUPERFICIAL TEMPORAL ARTERIES AND CERVICO-ENCEPHALIC AXES

ECHORTON

2015-A01552-47
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Version n°4 of 04/07/2017

Responsible
Poitiers University Hospital Center

Supervisory Directors:
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Dr Guillaume DENIS

Contents

Abbreviations

ACR	American College of Rheumatology
GCA	Giant cell arteritis
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
CRA	Clinical research associate
TA	Superficial temporal arteries
TAB	Temporal artery biopsy
CNIL	National Commission for Computing and Liberties
CPP	Committee for the Protection of Persons
CRF	Case Report Form
CRP	C-reactive protein
CSP	Public health code
CT	Corticosteroids
CDU	Color Doppler ultrasound
EULAR	European League Against Rheumatism
FDG	Fluorodeoxyglucose
GGT	Gamma glutamyl transpeptidase
PAL	Alkaline phosphatase
PET	Positron emission tomography
VPA	Vasculitis of the periadventicial vessels
SV	Sedimentation rate
VVV	Vasculitis of the vasa vasorum

Protocol Summary

2015-A01552-47

Version n°4 of 04/07/2017

TITLE	Validation of a diagnostic algorithm for giant cell temporal arteritis based on color Doppler ultrasound of the superficial temporal arteries and cervico-encephalic axes: ECHORTON
RESPONSIBLE	**Poitiers University Hospital Center**
SUPERVISING DIRECTORS	Dr. Christophe RONCATO Dr Guillaume DENIS
RATIONALE / CONTEXT	Giant cell arteritis (GCA) (or Horton's disease) is a vasculitis in the elderly, affecting medium and large caliber vessels. The diagnosis of GCA is a real challenge for the general practitioner or specialist. Since 1970, it has been based on a combination of clinical, biological and histological signs. Thus, the temporal artery biopsy (TAB), most often unilateral, was considered until recently as the reference method. Nevertheless, TAB poses many problems. As a result, research over the past 20 years has aimed to develop alternative diagnostic means to TAB. This has notably been the case with color Doppler ultrasound (CDU) since Wolfgang Schmidt's description of the halo sign. Although the European and British recommendations in force only position CDU in the second line, many authors mention the possibility of doing without TAB in a large number of cases. In addition, many practitioners who believe that it is not "ethical" to resort to an invasive procedure that is not very profitable, have already integrated CDU into their practice. However, no diagnostic algorithm validating this attitude, in a prospective series, has been published to date.
PRIMARY OBJECTIVE	Validation of a diagnostic algorithm for giant cell arteritis based on color Doppler ultrasound of the superficial temporal arteries, cervico-encephalic axes, axillaries and superficial femoral arteries used in 1st intention.
SECONDARY OBJECTIVES	1) Establish a probability model of the clinical and paraclinical score calculation type including at least the American College of Rheumatology (ACR) criteria, the CRP and the results of the Color Doppler ultrasound. 2) Determine the rate of “TAB positive” in the CDU “negative” and “doubtful” groups. Compare the GCA populations with CDU “positive” versus TAB “positive”.

	3) Describe the modifications of the Halo at W3/W4 and possibly correlate its persistence with a poorer clinical response. 4) Determine inter-observer variability/concordance for pathology and Doppler ultrasound examination. 5) Describe the cost-result of the algorithm
MAIN JUDGMENT CRITERIA	The number of patients with an alternative diagnosis within 2 years of follow-up among patients considered to have GCA on a clinical-biological suspicion + "positive" echo-Doppler.
SECONDARY JUDGMENTS CRITERION	1) To assess the criteria to be taken into account to establish a diagnostic score, the number of patients per collected variable will be determined according to the diagnosis of GCA confirmed or not. 2) The number of positive TAB will make it possible to calculate the rate of "positive TAB" in the "negative" CDU group. The frequency of vasculitis lesions of the vasa vasorum (VVV) and/or periadventicial vessels (VPA) will be established in this "negative" CDU group. Patients in the GCA group diagnosed by CDU will be compared to the group of GCA patients diagnosed by TAB for clinical and biological data. 3) The description of the evolution of the halos at W3/W4 will make it possible to study whether there is any correlation with the rate of corticosteroid-dependent patients, the number of relapses, ischemic complications, etc... 4) The number of TAB slide reading discrepancies will be established, and its corollary, the number of inter-operator discrepancies on the echo-Doppler. 5) Diagnostic costs (consultation and/or hospitalization, CDU and TAB), induced costs (complication, adverse event of TAB), avoided costs (absence of TAB for CDU positive patients), and indicators of efficacy (positive diagnosis rate according to the CDU, according to the diagnostic algorithm (CDU +/- TAB), number of Horton's disease successfully treated at 2 years of follow-up and the number of patients for whom the surgery could be avoided) will be determined.
METHODOLOGY / DIAGRAM OF THE STUDY	Diagnostic study in internal medicine, cross-sectional, prospective, regional multicenter.
SUBJECT INCLUSION CRITERIA	-Patient cared for in one of the participating centres: ≥ 50 years CRP supehigherTolaboratory normal Suspects of'GCA deend with: o Patients suspected of GCA according to the expert clinician and/or oAortitis or arteritis of one or more arteries originating from the aorta on imaging (angio-CT, angio-MRI or PET-CT18FDG) BenoteSecurityeSocial or in benoteficant by the'interimediary of'a third person having givenetheir participation agreement by understanding and accepting the constraints of the'estudy

	Free subject, without guardianship or curatorship or subordination
CRITERIA FOR NON-INCLUSION OF SUBJECTS	Patient who received a dose of corticosteroid therapy ≥ 20 mg of prednisone equivalent for more than 7 days in the month preceding inclusion Patient having undergone a temporal artery biopsy before carrying out a Doppler ultrasound Patient with a personal history of GCA Patient in the terminal palliative phase or suffering from a pathology or comorbidities such that the vital prognosis is committed at less than one year Patient with severe cognitive impairment Patient who cannot be monitored by the supervisor for the duration of the study (e.g. vacationers) Refusal to participate in the study Benefiting from enhanced protection, namely persons deprived of their liberty by a judicial or administrative decision, persons staying in a health or social establishment, adults under legal protection, and finally patients in an emergency situation. Patient participating in another clinical trial. Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (hormonal/mechanical: oral, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy)
PROCEDURE	Since the reliability of Doppler ultrasound is technical and operator-dependent, a preliminary meeting for the study will make it possible to verify the technical prerequisites, to train the participating operators and to define a consensus for the interpretation of the halos. In each of the centres, patients over 50 years of age with a clinical suspicion of GCA, established according to the levels of evidence described by the ACR recommendations, will be informed of the study by the supervising clinicians. Patients agreeing to participate will be cared for by clinicians who will respect the following diagnostic algorithm: In case of clinical suspicion of GCA, an CDU will be carried out within 7 days following the initiation of corticosteroids. The minimum biological assessment will consist of a blood count and a CRP assay. The diagnostic orientation criteria will be as follows: - l'observation of'a hypo haloeChogene net on two non-contiguous arterial segments will confirm the diagnosis of GCA, the patient will not undergo TAB. - In the event of a single halo, the patient will undergo a TAB (of cohyoueof the halo), of meme in the absence of a halo sign. If the TAB is positive, patients will be followed in the same way as patients with a positive CDU. If the TAB is negative, the diagnostic

	and therapeutic management of the patient will be left to the discretion of the doctor and noted in the follow-up. Clinical follow-up of patients will include at least one internist/rheumatologist and angiologist visit between 3 and 4 weeks after the start of corticosteroid therapy (for treated patients) and a 2nd CDU between 3 and 4 weeks after the start of corticosteroid therapy for patients whose 1st CDU was positive: - If a Halo is observedeon the axillaries and/or primitive carotids, a PET-CT-CT18FDG or an angio-CT of the aortic arch will be realiseto check for aortitis. - If the Halo persistsToS3/S4 (clinical significance is unknown), a visit to M3 with the same operator will be offered to the patient. Finally, internist/rheumatologist visits will be made at M3, M6, M12, M18, M24. To ensure the standardization and reproducibility of interpretation of the CDUs, 4 meetings bringing together the operators will be organized at 2 months, 6 months, 12 months and 18 months.
NUMBER OF PATIENTS	The objective is to include at least 100 patients carrying a Horton. It is therefore planned to include 168 people suspected of having gigantocellular arteritis.
LENGTH OF SEARCH	Duration of the inclusion period: 2 years Duration of participation of each subject: 2 years Data analysis duration: 6 months Total duration of the study: 4 years and 6 months
STATISTICS	Analysis of the primary endpoint will consist of determining the positive predictive value of CDU and the algorithm will be considered valid in the absence of alternative diagnoses within 2 years of follow-up in the group considered to have GCA on a clinical-biological suspicion + “positive” echo-Doppler. To establish a probability model of the clinical and paraclinical score calculation type, the variables significantly associated with the diagnosis will be determined by logistic regression. A number of points will be assigned to each variable based on the strength of its association with the diagnosis. The area under the ROC curve will be used as an indicator of the discriminative power of the score. Correlation analyzes will be carried out to study a possible link between the description of the halos and the persistence of a poorer clinical response and to assess the inter-operator reproducibility for the reading of the TAB slides and CDUs performed in 1st intention.
EXPECTED BENEFITS	The objective is to validate the diagnostic algorithm using CDU in 1st intention to confirm cases of GCA. The remaining place of the

	temporal artery biopsy will be specified. A predictive model including the result of the CDU will be proposed and will aim, after validation on other populations, to modulate the ACR score. This result will have a major impact in the daily practice of hundreds of doctors and patients per year in France, and will allow a reduction in the diagnostic delay.

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2. Scientific justification and general description of the research

2.1- Rationale for the study

Giant cellular arteritis (GCA) (or Horton's disease) is a vasculitis characterized histologically by an inflammation, most often transmural, made up of lympho-mono-macrophagic cells, sometimes of giant cells that can narrow the lumen of the artery and lead to thrombosis. It involves medium and large caliber vessels (preferential involvement of the branches of the external carotid, including the superficial temporal artery), but all the large arterial trunks may be involved, including the aorta (1, 2). GCA is the most common systemic vasculitis in Western countries. Its geographical distribution follows a frequency gradient which decreases from the north to the south of Europe. In France, its prevalence is around 1 per 1000 among the over 50s.

Indeed, GCA generally affects people over the age of 50, with a peak frequency between 70 and 80 years. A recent English work estimated the incidence of GCA at 1.2 per 10,000 patient-years, but 7.4/10,000 for women aged 70-79 years (3).

The diagnostic delay is sometimes several months (4, 5) while there is a visual risk with the possibility of irreversible blindness (10-15% of patients) and an increased risk of cardiovascular accident (6-8) .

Indeed, the diagnosis of GCA is a real challenge for the general practitioner or specialist. Since 1970, it has been based on a combination of clinical, biological and histological signs grouped together in part in the classification criteria of the American College of Rheumatology (9, 10).

Thus, the temporal artery biopsy (TAB), most often unilateral, was considered until recently as the reference method. Nevertheless, the TAB poses many problems:

- technical: invasive nature of the surgical procedure, sampling failure, local complications (abscess, hematoma, pain, nerve damage), management of anticoagulants, patient refusal
- logistical orders: accessibility of the operating room, extension of the hospitalization period
- diagnostic profitability: its sensitivity is imperfect with globally 20 to 30% of negative results. This result is partly due to the segmental and focal vascular tropism of the disease and to the existence of a more "proximal" form exclusively involving the aorta and its large trunks, but also to the difficulty of pathological diagnosis with an inter-observer variability not negligible (specimen size, number of cuts, doctor's experience, consideration of VVV and VPA (11-13). Thus, the result of the biopsy does not often influence the action to be taken by the practitioner (14) .

As a result, research over the past 20 years has aimed to develop alternative diagnostic means to TAB. This has notably been the case with color Doppler ultrasound since the description by Wolfgang A. Schmidt and collaborators of the halo sign on the superficial temporal arteries in 1995 (15).

Color Doppler ultrasound of ATS, subject to certain technical conditions (detailed later) and an experienced operator, is a non-invasive tool, at least as sensitive and very specific for the diagnosis of GCA as have shown well by recent studies and meta-analyses (16-18). A very recent study even showed a higher sensitivity of CDU compared to TAB for the diagnosis of GCA, 96% versus 67% for an identical specificity (119). CDU can additionally analyze other arterial segments potentially affected by disease. Thus the diagnostic performance of the CDU is further increased if the analysis concerns in addition to the ATS, the subclavian, axillary and common carotid arteries. (20).

Within the framework of a retrospective and monocentric study on the CH of La Rochelle (LR) we found results similar to those published with a sensitivity of 69% and a specificity of 100% of the CDU among 20 patients all suspected of 'GCA (13).

From critical reading of the scientific literature and our experience, we believe that the specificity problem of CDU becomes negligible if the pre-test probability is high, if systemic necrotic vasculitis has been ruled out, if the operator is experienced and if the CDU positivity criteria are strictly defined (example: certain and bilateral character of the Halo, hypoechoic character of the halo, not taking into account the effects of stenosis on the ATS).

The real limit of the CDU is undoubtedly its imperfect sensitivity. This could be due to certain histological phenotypes of GCA. Indeed, one study demonstrated the poor sensitivity of CDU in the event of isolated lesions of VVV and/or VPA compared to the classic florid attack of GCA, 20% versus 82.5% respectively (24).

This is why TAB could retain an important position in the event of a "negative" CDU.

Although the European and British recommendations in force only position CDU in the second line (25-27), many authors mention the possibility of doing without TAB in a large number of cases. In addition, many practitioners who believe that it is not "ethical" to resort to an invasive procedure that is not very profitable, have already integrated CDU into their practice (28-31). However, no diagnostic algorithm validating this attitude, in a prospective series, has been published to date.

Finally, we have shown that during hospitalization for suspected GCA, the delay in obtaining the ultrasound-doppler (and therefore the result) was shorter than the realization and the final rendering of the results of the biopsy of the temporal artery: 4.9 days on average for the CDU versus 7.2 days for the performance and 11.4 days for the result ($p < 0.001$) for the TAB, making it possible to shorten as much and in complete safety length of hospitalization (unpublished data). These preliminary data offer hope for improved cost-effectiveness and are also worth investigating in a prospective trial.

2.2. Summary of the benefits, if any, and the foreseeable and known risks for people undergoing research

2.2.1. Benefits

The expected benefit is to avoid systematic recourse to biopsy of the temporal artery. This could make it possible to shorten the diagnostic delay, reduce the duration of hospitalization and reduce the inconvenience associated with this surgical procedure.

2.2.2. Risks

The acts are performed and the products are used in the usual way, but specific monitoring procedures are provided for through this protocol.
The special monitoring methods do not entail any additional risk to the usual management

2.3. Declaration indicating that the research will be carried out in accordance with the protocol as well as good clinical practices and the legislative and regulatory provisions in force.

The person in charge and the supervisor also undertake that this research be conducted:

- in accordance with the protocol,
- in accordance with French and international good clinical practices currently in force,
- in accordance with the laws and regulations currently in force in France and internationally

2.4 References to scientific literature and relevant data serving as a reference for research

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3. Research objectives

3.1-Main objective

Validation of a diagnostic algorithm for giant cell arteritis based on color Doppler ultrasound of the superficial temporal arteries, cervico-encephalic axes, axillaries and superficial femoral arteries used in 1st intention.

3.2-Secondary objectives

1) Establish a probability model of the clinical and paraclinical score calculation type including at least the American College of Rheumatology (ACR) criteria, the CRP and the results of the Color Doppler ultrasound.
2) Determine the rate of "TAB positive" in the CDU "negative" and "doubtful" groups. Compare the GCA populations with CDU “positive” versus TAB “positive”.
3) Describe the modifications of the Halo at W3/W4 and possibly correlate its persistence with a poorer clinical response.
4) Determine inter-observer variability/concordance for pathology and echo-Doppler examination.
5) Describe the cost-result of the algorithm

4. Research design

4.1-Precise statement of the main evaluation criteria and, where applicable, the secondary evaluation criteria

4.1.1-Main evaluation criterion

The number of patients with an alternative diagnosis in the2 years of follow-up among patients considered to have GCA on clinical and biological suspicion + "positive" echo-Doppler.

4.1.2-Secondary evaluation criterion(ies)

1) To assess the criteria to be taken into account to establish a diagnostic score, the number of patients per collected variable will be determined according to the diagnosis of GCA confirmed or not.
2) The number of positive TAB will make it possible to calculate the rate of "positive TAB" in the "negative" CDU group. The frequency of vasculitis lesions of the vasa vasorum (VVV) and/or periadventicial vessels (VPA) will be established in this "negative" CDU group. Patients in the GCA group diagnosed by CDU will be compared to the group of GCA patients diagnosed by TAB for clinical and biological data.
3) The description of the evolution of the halos at W3/W4 will make it possible to study whether there is any correlation with the rate of corticosteroid-dependent patients, the number of relapses, ischemic complications, etc...
4) The number of TAB slide reading discrepancies will be established, and its corollary, the number of inter-operator discrepancies on the echo-Doppler.
5) Diagnostic costs (consultation and/or hospitalization, CDU and TAB), induced costs (complication, adverse event of TAB), avoided costs (absence of TAB for CDU positive patients), and indicators of efficacy (positive diagnosis rate according to the CDU, according to the diagnostic algorithm (CDU +/- TAB), number of Horton's disease successfully treated at 2 years of follow-up and the number of patients for whom the surgery could be avoided) will be determined.

4.2-Description of the research methodology

4.2.1-Experimental plan

Diagnostic study in internal medicine, cross-sectional, prospective, regional multicenter.

4.2.2-Procedure of the study

4.2.2.1-Inclusion

In each of the centres, patients over 50 with a clinical suspicion of GCA, established by the expert clinician, receive oral and written information concerning the protocol, its objectives and its constraints. A period of reflection is granted to the patients before collecting their non-objection to participate in the study.
The inclusion of the patient in the study will be mentioned in the patient file, it will specify the methods of collecting the non-objection as well as that of the information.

Patients agreeing to participate will be looked after by supervisors who will respect the diagnostic algorithm described below.
The minimum biological assessment will consist of a blood count and a CRP assay. The sedimentation rate (ESR), the assay of Gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) will be optional measurements.

The investigator assigns an identifier (number and initials) to the patient in order to guarantee the anonymization of the data.

This identifier will be in the following form:
Center number and patient number: I___I___I___I - I___I___I___I
Patient initials (Last name - First name):I___I - I___I

The patient number is given incrementally (ie in the order of the consent signatures).
The local investigator keeps a table of correspondence between the identity and the patient code, which will be destroyed at the end of the study.

4.2.2.2-Subject follow-up

DIAGNOSTIC ALGORITHM

Visit 1: Doppler echo examination

In case of clinical suspicion of GCA, an CDU will be carried out within 7 days following the initiation of corticosteroids.

Visit 2: consultation with the internist within 7 days after the Doppler ultrasound

The diagnostic orientation criteria will be as follows:

- The observation of a clear hypoechoic halo on two non-contiguous arterial segments will confirm the diagnosis of GCA, the patient will not undergo TAB.
- In the event of a negative CDU examination, the patient will undergo a TAB

Visit 3:consultation with the internist (maximum 3-4 weeks after initiation of corticosteroid therapy**)**

For patients with positive CDU n°1, a requested CDU n°2 (via a voucher informing the patient's participation), will be carried out between 3 and 4 weeks after the start of corticosteroid therapy:

- If a Halo is observed on the axillaries and/or primitive carotids, a PET-CT or injected CT will be performed to look for aortitis.
- If the Halo persists at W3/W4 (the clinical significance is unknown), a visit to M3 with the same operator (CDU n°3) will be offered to the patient.

For patients with negative CDU n°1, the results of the TAB will be collected:

- If this is positive, patients will be followed in the same way as patients with a positive CDU.
- If the TAB is negative:
    - Either Horton's diagnosis will be retained and the patient will have the same follow-up as those with a positive CDU or a positive TAB
    - Either an alternative diagnosis will be considered, and the diagnostic and therapeutic care of the patient will be left to the discretion of the doctor, and noted in a specific follow-up.

FOLLOW UP

Visits 4 (M3), 5 (M6), 6 (M12), and 7 (M24): follow-up consultation by the internist

Data on disease progression and treatment will be collected.
For patients with an alternative diagnosis, follow-up at M3, M12 and M24 can be done by telephone.

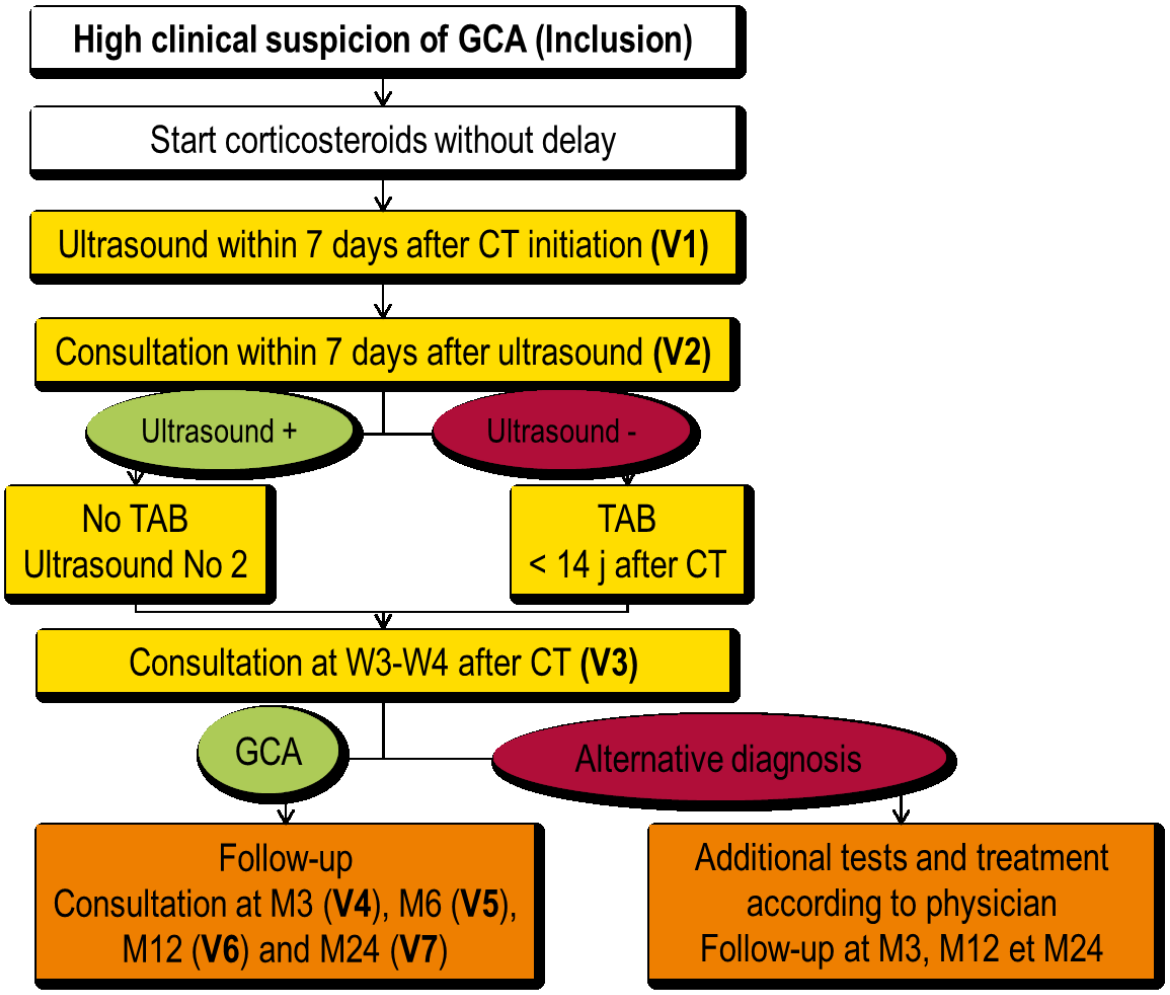

figure1: diagram of the diagnostic algorithm (GCA: giant cell temporal arteritis; TAB: temporal artery biopsy; CT: corticosteroid)

	V0 D0 inclusion	V1 < 7 d CT	V2 < 7 d of CDU	V3 3-4 weeks after CT	V4 M3	V5 M6	V6 M12	V7 M24
Information	X							
Consent	X							
Eligibility criteria	X							
Demography	X							
Clinical signs	X			X	X	X	X	X
Biology report	X					X	X	
Treatment	X		X	X	X	X	X	X
Support mode	X	X	X	X				
Arterial Doppler echo		X		X*	X*			
CDU or TAB appointment			X					
TAB result				X*				

Tableau 1: data collection schedule (* see diagnostic algorithm)

4.3-Description of the evaluation parameters and the methods to measure, collect and analyze these parameters

4.3.1-GCA diagnostic criteria according to the American College of Rheumatology 1990

1) Age greater than or equal to 50 years at onset of symptoms
2) Unusual headaches
3) Clinical abnormalities of the temporal arteries such as pain on palpation or decreased temporal pulse or claudication of the jaw
4) Increase in ESR > 50 mm at the 1st hour
5) Infiltrates of granulocytes or mononuclear cells with usually the presence of giant cells in the arterial wall

Probable diagnosis if 3 or more criteria
Sensitivity of 94% and specificity of 91%

4.3.2- Color Doppler Ultrasound Protocol

- Longitudinal and transverse examination of the bilateral subclavian, axillary, vertebral, superficial femoral and superficial temporal arteries.
- Blinding of the degree of clinical suspicion of the practitioner
- Duration of examination: 30 minutes, carried out as soon as possible after the request of the corresponding doctor (in practice within the following 48 hours according to our experience.)
- Ultrasound of the superficial temporal arteries (common trunk, frontal branch, parietal branch).
    - Type of ultrasound system: SIEMENS S2000 18L6 HD probe or Philips IU22 with L12-5 linear probe and Epiq 7G with L12-3 linear probe.

- Type of gel used: ECG contact gel & high conductivity defibrillator: Hypoallergenic, Water-soluble, Non-irritating, Non-corrosive, Non-abrasive.

- Arterial ultrasound cervico-encephalic axes (axillary, carotid, vertebral arteries) and axillary and superficial femoral. Probe type: 4-9 MHz
- Recording of a number of images or video of sufficient quality and on a suitable medium for proofreading, archiving on site.
- Diagnostic :
  - Positive if sign of the hypoechoic halo present on the 2 ATS or on 2 different arterial axes (example a vertebral and an ATS, or right and left primitive carotid).
  - Negative if doubtful standard examination
    - One-sided halo
    - Iso/hyperechoic halo
    - Halo seen on other arteries but normal temporal arteries
- Disregard "isolated strictures" on the ATS.
- Take into account thrombosis on ATS (before a TAB).
- Describe atheromatous plaques, carotid/axillary/subclavian/femoral stenoses).
- Blind review of the images (CDU n°1 and 2) by an expert: Dr RONCATO.

All patients with a "positive" echo-Doppler must be seen again by the same operator 3-4 weeks later, in order to determine the disappearance or persistence of the Halo; in case of persistence, it will be interesting to compare the echogenicity and to see the patient again at M3.

4.3.3- GCA processing protocol

No recommendations other than those of EULAR (The European League Against Rheumatism) and BSR/BHPR (25-27) for the starting dose and the corticosteroid tapering regimen (start between 0.5 and 1 mg/kg for 2 to 4 weeks, reduction for an objective of 15 to 20 mg of prednisone at 3 months, then more gradual reduction), idem vis-à-vis aspirin and the use of methotrexate.

Corticosteroid therapy can be started before Doppler ultrasound within a maximum period of < 7 days.

4.3.4- TAB protocol

Sampling :

- Performed < 14 days after start of corticosteroid therapy
- Size > 10mm
- Referred by ultrasound-Doppler or clinic if possible
- By a senior surgeon

Histological analysis:

- On the anapat voucher will be indicated the name of the protocol (ECHORTON), if the corticosteroid treatment was initiated and if so its start date.
- Fixing the biopsy specimen with 10% buffered formalin
- Measurement of the size of the fixed transmitted arterial segment
- Paraffin inclusion after salami every 3-4mm
- Staining with Hematoxylin Eosin Saffron (HES)
- Unsystematic Orcein or Van Gieson staining

- Preparation of numerous slides (thickness 3 µm) 8 levels until the block is exhausted

- Research :
  - inflammatory infiltrate, granuloma, giant cells (location of this infiltrate intima, media, adventitia)
  - of necrosis
  - fibrosis
  - calcification (location to be specified)
  - thickening of the intima
  - rupture, duplication of the internal elastic limit
  - vasa vasorum (VVV) lesion
  - lesion of vasculitis of the periadventicial vessels (VPA)
  - thrombosis
  - possible lesions of arteriosclerosis
  - possible amyloidosis lesion (Red-Congo not systematic)
  - Conclusion: GCA yes/no/doubtful/other
- Forwarding for proofreading of all the slides by an expert pathologist blind to the diagnosis retained by the initial pathologist: CHU de Poitiers

Collection of systematic adverse effects (at V3)

4.4- Expected duration of people's participation and description of the timing and duration of all periods of the trial, including follow-up, if applicable

Duration of inclusion: 24 months
Total duration of participation in the study for the patient: 24 months
Duration of analyses: 6 months
Estimated study duration: 54 months

From the first inclusion, the person in charge must immediately inform the competent authority and the CPP of the actual start date of the study.
The study end date will be sent by the person in charge to the CPP within 90 days. The end date of the research corresponds to the term of the participation of the last person who agrees to the research, or if applicable, to the term defined in the protocol.

4.5- Description of permanent or temporary stoppage rules

4.5.1- Termination of a person's participation in research

Subjects may withdraw their non-objection and request to leave the study at any time and for any reason.
In the event of premature discharge, the invigilator should document the reasons as fully as possible.
In the event of a lost subject, the supervisor will make every effort to reconnect with the person.

4.5.6- Stopping part or all of the search

The end of the research corresponds to the end of the participation of the last person who agrees to the research.

In the event of premature termination of the study, the information will be transmitted by the person in charge within 15 days to the CPP.

4.6- Identification of all the data to be collected directly in the observation notebooks, which will be considered as source data

A blank paper copy of the e-CRF can be printed from the e-CRF. The supervisor will therefore have the possibility of directly reporting the biological, clinical and radiological data of the patients included in it to facilitate data entry. The supervisor must date and sign this copy at the end of data collection.
This document will be an integral part of the patient's medical file and will be kept there permanently.
The data recorded in the e-CRF and coming from the source documents must be consistent with each other; otherwise, the differences must be justified and documented.

The rereading results of the TAB slides and Doppler echo images will be recorded in the e-CRF.

5. Selection and exclusion of persons from research

5.1- Inclusion criteria

- Patient cared for in one of the participating centers
- ≥ 50 years
- CRP higher than laboratory normal
- GCA suspects defined by:
    - Patients suspected of GCA according to the expert clinician and/or
    - Aortitis or arteritis of one or more arteries originating from the aorta on imaging (angio-CT, angio-MRI or PET-CT18FDG)
- Benefiting from Social Security or benefiting from it through a third party
- Having given their consent to participate by understanding and accepting the constraints of the study

5.2- Criteria for non-inclusion

- Patient who received a dose of corticosteroid therapy ≥ 20 mg prednisone equivalent for > 7 days in the month prior to inclusion
- Patient having undergone a temporal artery biopsy before carrying out an echo-doppler.
- Patient with a personal history of GCA
- Patient in the terminal palliative phase or suffering from a pathology or comorbidities such that the vital prognosis is committed at less than one year
- Patient with severe cognitive impairment
- Patient who cannot be monitored by the supervisor for the duration of the study (e.g. vacationers)
- Refusal to participate in the study
- Not benefiting from a Social Security scheme or not benefiting from it through a third party
- Benefiting from enhanced protection, namely persons deprived of their liberty by a judicial or administrative decision, persons staying in a health or social establishment, adults under legal protection, and finally patients in an emergency situation.
- Patient participating in another clinical trial.
- Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (hormonal/mechanical: oral, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy)

5.3- Recruitment methods

Patients followed in the internal medicine department of the participating centers and suspected of having giant cell arteritis will be offered to participate in the study.

5.4- Procedure for premature termination of research or exclusion of a person from research and procedure for monitoring the person

The withdrawal of a patient from the study will in no way change his usual care in relation to his illness. In the event of an adverse event, whether serious or not, precise monitoring may be considered depending on the seriousness of the adverse event and the severity. In the context of a withdrawal of non-objection, the data collected will not be used in accordance with the patient's wishes.

6- Safety assessment

6.1- Procedures put in place for the recording and notification of adverse events

The occurrence of an Adverse Effect related to the treatment of the patient during this protocol will give rise to a declaration in the appropriate vigilance system (pharmacovigilance, biovigilance, haemovigilance, materiovigilance, etc.).

6.2- Supervisory Committee

Not planned.

7.- Statistics

7.1- Description of planned statistical methods, including schedule of planned interim analyzes

All the parameters collected will be presented in tables and diagrams containing descriptive statistics for each of the sub-populations (confirmation or not of GCA), as well as for the entire population analyzed, according to the following methods:

- for the quantitative variables: the number of missing values and non-missing values, the mean, the standard deviation, the 95% confidence interval, the median, the 1st quartile, the 3rd quartile, the minimum and the maximum,
- for qualitative variables: the number of missing values and non-missing values, frequencies, percentages and 95% confidence intervals, for each of the modalities of the variable.

The analysis of the primary endpoint will consist of determining the positive predictive value of CDU and the algorithm will be considered valid in the absence of an alternative diagnosis within 2 years of follow-up in the group considered to have GCA. on a clinical-biological suspicion + “positive” echo-Doppler.
To establish a probability model of the clinical and paraclinical score calculation type, the variables significantly associated with the diagnosis will be determined by logistic regression. A number of points will be assigned to each variable based on the strength of its association with the diagnosis. The area under the ROC curve will be used as an indicator of the discriminative power of the score.
Correlation analyzes will be carried out to study a possible link between the description of the halos and the persistence of a poorer clinical response and to evaluate the inter-operator reproducibility for the reading of the TAB slides and Doppler echo images.
The analysis of diagnostic costs, induced costs, avoided costs, and efficiency indicators will make it possible to determine the costs/results of the diagnostic algorithm.

7.2- Expected number of people to be included in the research, and expected number of people in each research location with its statistical justification

According to a retrospective study of 42 patients treated for suspected Horton's disease, 70% of them had their Horton's diagnosis confirmed. To include at least 100 patients with Horton's disease over the study period, it is therefore necessary to include at least 142 patients suspected of Horton's disease (100 confirmed Horton's/42 other diagnoses). To take into account the possible overestimation of confirmed cases of Horton's disease due to biases of the retrospective study, the objective is to include 168 patients suspected of Horton's disease.
The population over 50 represents just over one million inhabitants in Charente-Maritime, Deux-Sèvres and Vienne. Considering an incidence of 1.2/10,000 inhabitants, approximately 120 new cases of Horton are detected each year.

Department	Number of people over 50	Number of new cases of Horton per year	Number of new Horton cases over 24 months	Estimation of the number of suspected cases of Horton over 24 months
Charente Maritime	491 871	59	118	168
Vienna	284,078	34	68	97
Two Sevres	261 272	31	63	90
Total	**1037221**	**124**	**249**	**355**

Table 2: theoretical recruitment potential

Knowing that the diagnosis of GCA is difficult, the majority of patients likely to be carriers of Horton are referred to clinicians. However, to account for patients not cared for by monitors participating in the study and patients refusing to participate, the goal is to include 45-50% of suspected Horton cases.

Center	Recruitment objective (Nb patients/month)	Duration of inclusion (months)	Forecast over the entire duration of the study
La Rochelle	2	24	48
Rochefort	1.5	24	36
Poitiers	2	24	48
Niort	1.5	24	36
Angouleme	1	24	24
Nantes	2	12	24

Table 3: goal of inclusion

7.3- Expected degree of statistical significance

The statistical tests will be carried out at the bilateral alpha risk of 5%.

7.4- Statistical criteria for stopping research

An interim analysis at 1 year of the start of inclusions will be made. Depending on the results (absence or presence of an alternative diagnosis in the group considered to have GCA on a clinical-biological suspicion + “positive” echo-Doppler) the study will be continued or not.

7.5- Method for taking into account missing, unused or invalid data

In case of premature termination and non-compliance with the protocol, the reasons will be documented. Missing data will be described in terms of numbers and corresponding percentages for each criterion and at each visit. There are no plans to replace patients exiting the study.
Patients suspected of Horton's disease are treated with corticosteroids. The administration of this treatment requires regular dose reviews. Patients are therefore monitored regularly in current practice and few loss of follow-up are expected in the study. On the other hand, cortisone treatment allows a good clinical evolution in patients with gigantocellular arteritis and the response to treatment in the very old subject seems comparable to that of the younger subject. The expected death rate is therefore that of the general population of the same age. Thus, if less than 5% of the patients in the study are lost to follow-up or died, the missing data will be replaced by deductive imputation when possible (e.g. patients with a combination of clinical signs, biological and examinations in favor of a horton and a good evolution under corticosteroids will be classified as suffering from Horton's disease). In the event of a higher rate of missing data, other methods of managing problematic data will be considered.

7.6- Management of modifications made to the analysis plan of the initial strategy

Not provided in research.

7.7- Choice of people to include in the analyzes

All eligible and evaluable subjects will be included in the analyses.

8- Justification of the request for validation of research in Routine Care

Given all of these elements, the research manager qualifies this research as first-line research in routine care, since:

- all acts are performed and products used in the usual way
- research is indeed to evaluate diagnostic tests (TAB and CDU) which are in common practice, ie subject to professional consensus in respect of their indications.

1) This research does not cover innovative or obsolete techniques or strategies.
2) The combination of acts is not an innovative combination.
3) The research does not relate to the comparison of two medical strategies

Finally, the particular methods of implementation in research, the order in which the diagnostic examinations are carried out, represent negligible constraints for the person who takes part in the research. (Article R 1121-3 of the Public Health Code (CSP), Decree No. 2006-477 of April 26, 2006)
The person in charge of the research will therefore submit, before any implementation of the research, for a favorable opinion and confirmation of the qualification of the research, the study protocol to the Committee for the Protection of People West III, in accordance with article L 1121-1 of the CSP as they result from laws n° 2004-806 of August 9, 2004 and n° 2006-450 of April 18, 2006 relating to public health policy.

9.-Right of access to source data and documents

9.1- Access to data

People participating in this research will be informed of their right to access and rectify data concerning them as well as the terms of application of this right via the newsletter.
Only personnel authorized by the manager (supervisors, ARC, TEC) and representatives of health authorities may have access to this information, without breaching confidentiality and within the limits authorized by laws and regulations.
The source documents will consist of all the information, results of examinations appearing in the medical records of the people participating in this research.

9.2- Source documents

If necessary, the responsible person's affiliated organization may request direct access to the medical file for verification of the procedures and/or research data, without breaching confidentiality and within the limits authorized by laws and regulations.

9.3- Data confidentiality

By signing this protocol, the supervising directors and all the associated supervisors undertake to keep the identities of the subjects who participated in the study confidential.
These people, in the same way as the supervisors themselves, are subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).
During the research or at its end, the data collected on the people who agree to it and transmitted by the interveners will be made anonymous.
Under no circumstances should they clearly show the names of the persons concerned or their addresses.
On the observation notebooks, each subject will be identified by a code comprising successively the first letter of the surname and first name, the mention of the code of the center followed by a 3-digit number.
This code will be the only information which will appear on the observation book (CRF) and which will make it possible to attach the CRF to the subject a posteriori.
The person in charge of the research is also required to code the patient data on all the documents that he may have in his possession which would be attached to the CRF.

10- Quality control and assurance

The Manager will ensure the proper completion of the study, the collection of the data generated in writing, their documentation, recording and report, in accordance with the legislative and regulatory provisions in force.

The supervising director and the members of his team agree to make themselves available during the Quality Control visits carried out at regular intervals by the Manager.

During these visits, the following elements will be reviewed:
- Non-objection form
- Compliance with the study protocol and the procedures defined therein
- Finalization of study documents (observation book, etc.) and circuits between the various stakeholders
- Setting up the study in the associated centers
- Quality of data collected in the observation book: accuracy, missing data, consistency of data with "source" documents (medical records, appointment books, original laboratory results, etc.)
- Monitoring of the study in the participating centers

If a differential quality control (ie level of quality control depending on the risk incurred by the subjects of the study) is set up, specify the methods.
On the other hand, supervisors undertake to accept the quality assurance audits carried out by the person in charge.

All data, all documents and reports may be subject to regulatory audits and inspections without medical secrecy being invoked.

11.-Ethical considerations

11.1- Committee for the protection of persons

The person in charge of the research undertakes to submit the study project to the prior authorization of the Committee for the Protection of Persons West III.. The information communicated relates firstly to the methods and nature of the research and to on the other hand, on the guarantees provided for the participants in this trial.

Notification of the CPP's favorable opinion will be sent to the person in charge of the study

11.2- Substantial changes

In the event of a substantial modification made to the protocol by the invigilator, it will be approved by the person in charge.
Any substantial modification to the study protocol must be notified to the Committee for the Protection of Persons in order to verify that the proposed modifications do not at any time alter the guarantees given to the people who take part in the research.
Prior to its implementation, the latter must obtain a favorable opinion from the CPP.

11.3- Information of persons

Patients will be informed in a complete and fair manner, in understandable terms, of the objectives and constraints of the study, of their rights to refuse to participate or that their relatives refuse their participation in the study or of the possibility of withdrawing. at any time.
All this information appears on an information and non-objection letter given to the subject.
The non-objection form will be collected by the supervisor, or a doctor who represents him before the definitive inclusion in the study.
A copy of the non-objection form signed by the invigilator will be given to the patients, the invigilator will keep the original in the center binder.

11.4- Indemnification of subjects

No compensation is provided

12- Data processing and retention of documents and data

12.1- Observation notebook

A case report (CRF) will be created for each subject. All information required by the protocol will be provided in the CRF.
The people responsible for filling in the CRFs (the supervisor, TEC, etc.) will be identified in the table of delegations of responsibilities for each center (kept in the center binder).
An Internet data collection medium, developed by the manager, will be used in the context of this study.
This electronic observation book will be set up in each of the centres.
It only requires an internet connection and a browser. A help document for the use of this tool will be provided to supervisors.
The data consistency check tests will be integrated in electronic format.
An audit function is integrated into the electronic notebook, thus making it possible to follow any modification of study data. This function also makes it possible to clearly identify the person who made the modification as well as the date. A justification can possibly be integrated in comment.

12.2- Computerized data and submission to the CNIL

The data collected during the study will be kept in a computer file respecting the law "Informatique et Libertés" of January 6, 1978 amended in 2004. The person in charge will send a request for an opinion to the Consultative Committee on the Processing of Information in research in the field of health (CCTIRS) and a request for authorization from the National Commission for Computing and Freedoms (CNIL). The data will be processed and computerized anonymously and confidentially on a secure system.

12.3- Archiving

The following documents will be archived by the radiology department of the Groupe Hospitalier de la Rochelle Ré Aunis until the end of the period of practical usefulness.
This indexed archive includes:

- Copies of the authorization letter from the CNIL and the mandatory opinion from the CPP and the CCTIRS
- The successive versions of the protocol (identified by the version number and the version date),
- The completed and validated observation book for each subject included,
- All appendices specific to the study,
- The final report of the study resulting from the statistical analysis and the quality control of the study (double sent to the person in charge).
- Any audit certificates produced during the research

The database that gave rise to the statistical analysis must also be archived by the person in charge of the analysis (paper or electronic medium).
At the end of the period of practical usefulness, all the documents to be archived will be placed under the responsibility of the manager for 15 years after the end of the study in accordance with institutional practices.

No displacement or destruction can be carried out without the agreement of the person in charge. At the end of the 15 years, the person in charge will be consulted for destruction. All data, documents and reports are subject to audit or inspection.

13.- Financing and insurance

13.1- Study budget

The costs related to this research are as follows:

- Medical time for:
  - Kick-off meeting for supervisors and collaborators
  - 5 consultation meetings for CDU operators
  - Anatomo-pathologist review time
- TEC time for logistics support
- Statistician time
- Medical-technical acts: CDU n°2 and 2nd set of TAB blades
- Materials: box for anapath slide, labels
- Miscellaneous expenses: meetings, coordinator missions, stationery, miscellaneous mailings, publication, etc.

This project is funded following its selection by the scientific committee of the Poitou-Charentes regional call for tenders (budget: 60k€).

13.2- Insurance

Insofar as the research is well qualified as Routine care research by the requested CPP, which means the absence of additional risk linked to the study, the insurance will be that of the establishment responsible for the care (article L. 1142-2).

14- Feasibility of the study and expected benefits

14.1- Feasibility

Promotion

- Mrs. Véronique FERRAND-RIGALLAUD and Mrs. Fanny ABRIAT ensure the stages of promotion of the project on behalf of the manager.

Coordination

- Dr RONCATO and Dr DENIS are the scientific managers of the project.
- Mrs ALLIX-BEGUEC provides support for the coordination of the project

Investigation

Supervisors of the University hospital of Poitiers, and the hospital of Nantes, Niort, Angouleme, Rochefort and La Rochelle with patients suspected of GCI in their active file have agreed to participate (list of centers and associated supervisors).

The angiologists of the same establishments gave their agreement to participate and follow the training meetings on the detection of the halo by CDU. Indeed, the reliability of Doppler ultrasound being technical and operator-dependent, a meeting preliminary to the study will make it possible to verify the preliminary technical conditions, to train the participating operators and to define a consensus for the interpretation of the halos. Then, to ensure the standardization and reproducibility of interpretation of the CDUs, 4 meetings bringing together the operators will be organized at 2 months, 6 months, 12 months and 18 months.

Pathologists from the University Hospital of Poitiers, Nantes, Niort, Angouleme, Rochefort and La Rochelle have agreed to participate.

Prof. GOUJON gave his agreement to supervise the proofreading of all the TAB slides of the patients included in the study.

The supervisors will be helped by TEC/ARC of the CHU of Poitiers, and the CH of Nantes, Niort, Angouleme, Rochefort and La Rochelle.

14.2-Expected benefits

The objective is to validate this diagnostic algorithm using CDU in 1st intention to confirm cases of GCA. The remaining place of the temporal artery biopsy will be specified. A predictive model including the result of the CDU will be proposed and will aim, after validation on other populations, to modulate the ACR score. This result will have a major impact in the daily practice of hundreds of doctors and patients per year in France.

15- Rules relating to publication

The communications and scientific reports corresponding to this study will be carried out under the responsibility of the supervising directors of the study with the agreement of the responsible supervising directors. The co-authors of the report and publications will be thesupervisorsand the practitioners and pathologists involved, in proportion to their contribution to the study, as well as the biostatistician and the associated researchers.
Publication rules will follow international recommendations (N Engl J Med, 1997; 336:309-315).

16- List of appendices

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Humans

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (addition of note of clarification)
55th WMA General Assembly, Tokyo, Japan, October 2004 (addition of note of clarification)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble
1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles applicable to medical research involving humans, including research on human biological material and identifiable data.
The Declaration is designed as an inseparable whole. Each paragraph must be applied in conjunction with all other relevant paragraphs.

2. In accordance with the mandate of the WMA, this Declaration is primarily addressed to physicians. However, the WMA invites others engaged in medical research involving humans to adopt these principles.

General principles
3. The WMA's Geneva Declaration commits physicians to "My patient's health shall prevail over all other considerations" and the International Code of Medical Ethics states that a "physician shall act in the best interest of the patient when caring for him".

4. The physician's duty is to promote and safeguard the health, well-being and rights of patients, including those involved in medical research. The doctor devotes his knowledge and conscience to the fulfillment of this duty.

5. Medical progress is based on research, which ultimately must involve human beings.

6. The primary objective of medical research involving human beings is to understand the causes, development and effects of disease and to improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions need to be continuously evaluated through research into their safety, effectiveness, appropriateness, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human beings and protect their health and rights.

8. If the primary objective of medical research is to generate new knowledge, this objective should never prevail over the rights and interests of those involved in the research.

9. It is the duty of physicians engaged in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of information of those involved in the research. The responsibility to protect people involved in research should always rest with a doctor or other healthcare professional and never with people involved in research, even if they have given their consent.

10. In medical research involving human beings, doctors must take into account the ethical, legal and regulatory norms and standards applicable in their own country as well as international norms and standards. The protections guaranteed by this Statement to persons involved in research cannot be restricted or excluded by any ethical, legal or regulatory provision, national or international.

11. Medical research should be conducted in such a way as to minimize possible harm to the environment.

12. Medical research involving human beings should be conducted only by persons who have acquired appropriate education, training and qualifications in ethics and science. Research involving healthy patients or volunteers requires the supervision of a physician or other qualified and competent healthcare professional.

13. Appropriate opportunities to participate in medical research should be offered to groups that are under-represented in it.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that it is justified by its potential value in prevention, diagnosis or treatment and if the physicians have good reasons to believe that participation in research will not harm the health of the patients concerned.

15. Adequate compensation and treatment must be guaranteed for people who have suffered harm as a result of their participation in research.

Risks, Constraints and Benefits
16. In medical practice and medical research, most interventions involve risks and harms.
Medical research involving human beings can only be conducted if the importance of the objective outweighs the risks and inconveniences for the people involved.

17. Any medical research involving human beings must first be the subject of a careful assessment of the foreseeable risks and disadvantages for the persons and groups involved, in relation to the foreseeable benefits for them and the other persons or groups affected by the disease. pathology studied.
All measures intended to reduce the risks must be implemented. Risks must be constantly monitored, assessed and documented by the researcher.

18. Physicians cannot engage in research involving human beings without being certain that the risks have been properly assessed and can be satisfactorily managed.
When the risks prove to outweigh the potential benefits or once definitive conclusions have been demonstrated, physicians must assess whether to continue, modify or immediately cease research.

Vulnerable populations and individuals
19. Certain groups or individuals being researched are particularly vulnerable and may have a greater likelihood of being abused or suffering additional harm.
All vulnerable groups and individuals should benefit from adequate protection.

20. Medical research involving a vulnerable group is only justified if it meets the health needs or priorities of that group and cannot be carried out on a non-vulnerable group. In addition, this group should benefit from the resulting knowledge, practices or interventions.

Scientific requirements and research protocols
21. Medical research involving human beings must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, on other relevant sources of information and on appropriate laboratory experiments and, where appropriate , about animals. The welfare of animals used in research must be respected.

22. The design and conduct of all research involving humans should be clearly described and justified in a research protocol.
This protocol should contain a statement of the ethical issues in question and indicate how the principles of this Statement have been taken into consideration. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for those involved in the research, and information regarding measures planned to treat and/or compensate those who have suffered harm as a result of their participation in research.
In clinical trials, the protocol should also mention appropriate arrangements for access to the tested intervention after the clinical trial.

Research Ethics Boards
23. The research protocol must be submitted to the relevant research ethics committee for review, comment, advice and approval before the research begins. This committee must be transparent in its operation, must be independent of the researcher, sponsor and any other undue influence and must be duly qualified. It must take into account the laws and regulations of the country or countries where the research is taking place, as well as international norms and standards, but these must not allow the restriction or exclusion of any of the protections guaranteed by this Declaration to people involved in the research.
The committee must have the right to monitor ongoing research. The researcher must provide the committee with information on the follow-up, in particular concerning any serious adverse event. No changes can be made to the protocol without evaluation and approval by the committee. At the end of the research, the researchers must submit to the committee a final report containing a summary of the findings and conclusions of the research.
Privacy and Confidentiality
24. Every precaution should be taken to protect the privacy and confidentiality of personal information concerning those involved in research.

Informed consent
25. The participation of persons capable of giving informed consent in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no person

capable of giving informed consent should be involved in research without having given free and informed consent.

26. In medical research involving persons capable of giving informed consent, any person who may potentially be involved must be properly informed of the researcher's objectives, methods, sources of funding, any possible conflicts of interest, institutional affiliations , the expected benefits and potential risks of the research, the inconveniences it may cause, the measures that will be taken after the clinical trial and any other relevant aspect of the research. The person potentially involved in the research must be informed of their right to refuse to participate or to withdraw from it at any time without retaliation. Careful consideration should be given to the specific information needs of each person who may potentially be involved in the research and to the methods adopted to provide the information. When the doctor or another person qualified in the field is certain that the person concerned has understood the information, he must then seek his free and informed consent, preferably in writing. If consent cannot be given in writing, unwritten consent must be formally documented in the presence of a witness. he must then seek his free and informed consent, preferably in writing. If consent cannot be given in writing, unwritten consent must be formally documented in the presence of a witness. he must then seek his free and informed consent, preferably in writing. If consent cannot be given in writing, unwritten consent must be formally documented in the presence of a witness.
All persons involved in medical research should have the choice of being informed of the general conclusions and results of such research.

27. When seeking informed consent from a person for participation in research, the physician must be particularly attentive when the latter is in a relationship of dependence with him or could give consent under duress. In this case, informed consent must be sought by a person qualified in the matter and completely independent of this relationship.

28. When the research involves a person incapable of giving informed consent, the doctor must seek the informed consent of his legal representative. Incapable people should not be included in research that is unlikely to benefit them unless it is intended to improve the health of the group they represent, that it cannot be done with capable people to give informed consent and that it entails only minimal risks and inconveniences.

29. When a person considered incapable of giving informed consent is able to give his assent concerning his participation in research, the doctor must seek this assent in addition to the consent of his legal representative. The refusal of the person potentially involved in the research should be respected.

30. Research involving persons who are physically or mentally incapable of giving consent, for example unconscious patients, may be conducted only if the physical or mental condition precluding giving informed consent is a necessary characteristic of the group to which the research relates. .
In such circumstances, the doctor must seek the informed consent of the legal representative. In the absence of a legal representative and if the research cannot be delayed, it can be launched without informed consent. In this case, the research protocol must mention the specific reasons for involving people whose condition renders them incapable of giving their informed consent and the research must be approved by the relevant research ethics committee. Consent to maintain the person concerned in the research must, as soon as possible, be obtained from the person himself or from his legal representative.

31. The physician must provide full information to the patient on the nature of the research-related care. A patient's refusal to participate in research or his decision to withdraw should never harm the patient-physician relationship.

32. For medical research using tissues or data of human origin, such as research on tissues and data contained in biobanks or similar repositories, physicians must seek informed consent for their analysis, storage and/or reuse . There may be exceptional situations where it is impractical or even impossible to obtain consent. In such situations, research may be undertaken only after review and approval by the relevant research ethics board.

Placebo use

33. The benefits, risks, harms, and effectiveness of a new intervention should be tested and compared with those of proven best interventions, except in the following circumstances:
when there is no proven intervention, the use of placebo, or no intervention, is acceptable; Or when for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of a placebo, or no intervention, is necessary in order to determine the efficacy or safety of a intervention, and when patients receiving an intervention less effective than the best proven intervention, placebo, or no intervention, are not at additional risk of serious or irreversible harm from not having received the best proven intervention.
The greatest care must be taken to avoid any abuse of this option.

Conditions of access to the intervention tested after the clinical trial

34. In preparation for a clinical trial, sponsors, researchers and host governments should make arrangements for all participants who still need access to an intervention identified as beneficial in the trial. after this one. This information should also be communicated to participants during the informed consent process.

Recording of research, publication and dissemination of results

35. Any research involving human beings must be registered in a publicly accessible database before the first person involved in the research is recruited.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations regarding the publication and dissemination of research results. Researchers have a duty to make available to the public the results of their research involving human beings. All parties are responsible for providing complete and accurate reports. They should adhere to accepted ethical guidelines for writing reports. Both negative and inconclusive and positive results should be published or otherwise made public. The publication must mention the sources of funding, institutional affiliations and conflicts of interest.

Interventions not proven in clinical practice

37. In the context of the treatment of a patient, in the absence of proven interventions or lack of effectiveness of these interventions, the doctor, after having sought the advice of experts and with the informed consent of the patient or his legal representative, may resort to an unproven intervention if, in his professional judgment, it offers a chance of saving the life, restoring health or alleviating the suffering of the patient. This intervention should subsequently be the subject of research to assess its safety and effectiveness. In any case, the new information must be recorded and, where appropriate, made public.