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Original article

Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA)

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ABSTRACT

Purpose. – Management of giant cell arteritis (GCA, Horton's disease) involves many uncertainties. This work was undertaken to establish French recommendations for GCA management.
Methods. – Recommendations were developed by a multidisciplinary panel of 33 physicians, members of the French Study Group for Large Vessel Vasculitis (*Groupe d'étude français des artérites des gros vaisseaux* [GEFA]). The topics to be addressed, selected from proposals by group members, were assigned to subgroups to summarize the available literature and draft recommendations. Following an iterative consensus-seeking process that yielded consensus recommendations, the degree of agreement among panel members was evaluated with a 5-point Likert scale. A recommendation was approved when ≥ 80% of the voters agreed or strongly agreed.

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Results. – The 15 retained topics resulted in 31 consensus recommendations focusing on GCA nomenclature and classification, the role of temporal artery biopsy and medical imaging in the diagnosis, indications and search modalities for involvement of the aorta and its branches, the glucocorticoid regimen to prescribe, treatment of complicated GCA, indications for use of immunosuppressants or targeted biologic therapies, adjunctive treatment measures, and management of relapse and recurrence.
Conclusions. – The recommendations, which will be updated regularly, are intended to guide and harmonize the standards of GCA management.

Giant cell arteritis (GCA), also called Horton's disease in French terminology, is a vasculitis of large-sized vessels of unknown etiology. This rare disease predominantly affects women, northern Europeans and people over 50 years of age, with its incidence peaking between 70 and 80 years. Clinically, GCA bears a risk of sudden vision loss and increased intermediate and long-term cardiovascular morbidity and mortality [1–3]. GCA is diagnosed and treated in hospitals and private practice [4].

Numerous uncertainties persist with regard to optimal GCA management. GCA diagnosis based on temporal artery biopsy (TAB) and glucocorticoid-treatment regimens [2,3] are not completely defined. In addition, the advent of modern vascular imaging techniques and the description of new therapeutic agents and strategies have led to diverse management protocols. The literature on these subjects is difficult to interpret because of discordant findings and the lack of robust studies.

These considerations prompted the French Study Group for large vessel vasculitis (*Groupe d'étude français des artérites des gros vaisseaux* [GEFA]) to devise recommendations for GCA management. The objectives were to reach consensus among experts' diverse practices and to propose guidelines for hospital physicians and less specialized private practitioners.

1. Material and methods

1.1. Study group

A panel of GEFA members developed the recommendations. The GEFA is mostly composed of teaching hospital physicians specialized in internal medicine who share an interest in managing and conducting research on GCA. An initial panel of 14 experienced "senior" GEFA members volunteered to participate in this project. After the "initial panel" had selected the topics to be addressed, it designated 7 "junior" physicians, all internists or trainees in internal medicine, whose specific task was to help with the literature search. In addition, a radiologist, a pathologist and a nuclear medicine specialist with practical experience in GCA management agreed to join the "enlarged panel" to help on one or several topics. Subsequently, the panel was completed by the addition of 9 other senior GEFA members (8 internists, 1 rheumatologist) who responded positively to an invitation to take part in it. These additional participants were asked to give their independent opinions on the literature synthesis and the proposed recommendations. All 33 physicians of the "final panel" worked in university hospitals or tertiary care centers. Several panel members were also vascular medicine specialists and 1 worked in an ophthalmologic hospital.

A 5-member Steering and Writing Committee of senior panel members (BB, KHL, ML, LS, AM) was responsible for organizing and managing face-to-face meetings, e-mail correspondence, preparation and distribution of the iterative versions of the written documents, electronic polling, searching the literature to identify relevant publications during the development of the recommendations, and manuscript preparation.

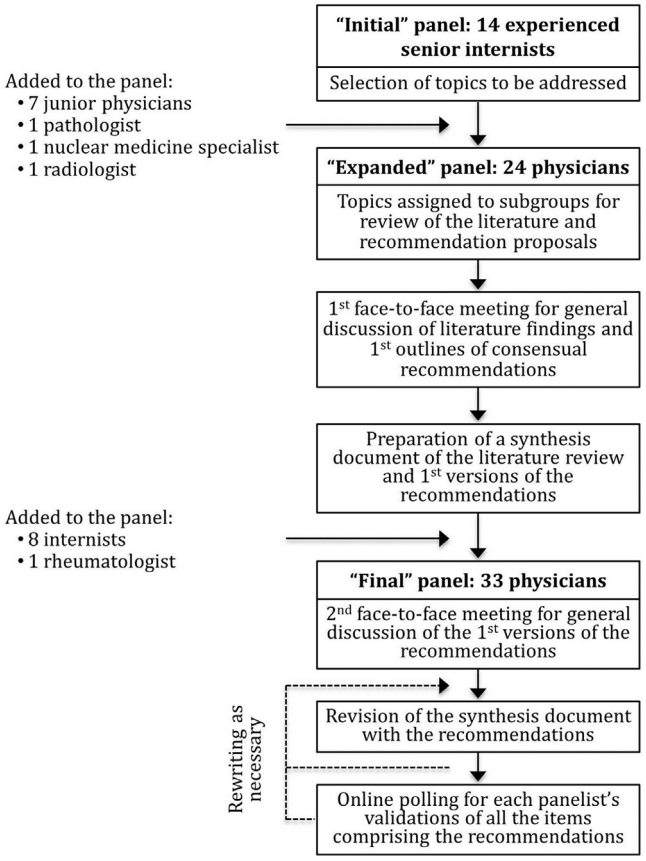

Fig. 1. Schematic diagram of the procedure used to obtain the consensual GCA recommendations.

1.2. Development of recommendations

Fig. 1 outlines the main stages of the procedure followed to develop recommendations. The 14 initial panel members agreed on the topics via e-mail exchanges. The topics proposed by a panel member were discussed and the final selection was based on the following criteria: 1) has an impact on clinical practice; 2) has resulted in publications of original data; and 3) could benefit from standardized practices because of discordance among practitioners. For each selected topic, a definition of the question and the objectives of the recommendation were drafted. The topics were assigned to subgroups of 2 or 3 senior physicians and 1 or 2 junior physicians; the topic distribution took into consideration the preferences expressed by the senior members. Subgroups were instructed to conduct a systematic literature review focusing on articles published during the past 20 years, to write a summary of the literature and to propose 1 or more outlines for recommendations. Subgroups had 3 months to complete this task.

Table 1
Topics retained for the development of recommendations and objective of each recommendation.

No.	Topic	Statement of objectives
1	Terminology	Decide on the name(s) to use to designate giant cell arteritis (GCA)
2	Nomenclature and classification	Decide on the definition and classification system to adopt for GCA
3	Clinical diagnosis	Decide under what circumstances a clinical diagnosis of GCA is acceptable or requires confirmation by additional diagnostic tests
4	Temporal artery biopsy (TAB)	Determine the role of TAB (and how it should be obtained and processed) in the diagnostic work-up for GCA
5	Temporal artery imaging	Determine the roles of temporal artery imaging and the technique(s) to be used in the diagnostic work-up for GCA compared to TAB
6	Imaging of the aorta and its branches to diagnose GCA	Determine the roles of imaging of the aorta and its branches in the diagnostic work-up for GCA and the technique(s) to be used compared to TAB
7	Biomarkers	Define which biomarkers are useful for GCA diagnosis and follow-up
8	Search for aortic complications	Decide the rationale and imaging modalities to screen for complications of aortic involvement in patients with established diagnoses of GCA
9	Glucocorticoid treatment of uncomplicated GCA (i.e., without ophthalmic involvement and without arteritis of the aorta or its branches)	Define the glucocorticoid regimen for the treatment of uncomplicated GCA
10	Treatment of GCA with ophthalmic involvement	Define the treatment of GCA (or suspected GCA) with ophthalmic involvement
11	Treatment of GCA with aortoarteritis	Define the treatment of GCA with involvement of the aorta or its branches
12	Adjunctive immunosuppressant or immunomodulatory therapy	Define the indications and regimens for the use of adjunctive immunosuppressive or immunomodulatory agents to treat GCA
13	Targeted biologic therapies	Define the role of targeted biologic therapies in the treatment of GCA
14	Aspirin, anticoagulants and statins	Define the usefulness of low-dose aspirin or other adjuvant therapies during GCA and define their indications and prescription regimens
15	Treatment of relapse and recurrence	Define the treatment of GCA relapse or recurrence

The consensus-seeking process was based on a modified nominal group technique [5] and consisted of 2 face-to-face meetings held 6 months apart. During the first meeting, the subgroups presented their syntheses of literature findings and 1 or more proposals for recommendations for the topic(s) treated. This information and the proposals were debated and the panel decided which recommendations could be proposed for each topic. After that meeting, a "synthesis document" was prepared, consisting of a summary of the findings reported in the literature review and drafted recommendations for each topic, which was sent to all panel members before the second meeting. During the second meeting, each proposed recommendation was thoroughly discussed, and the group decided the need for and types of modifications required. After the second meeting, the recommendations were revised in accordance with the outcomes of those discussions. Questions with consensus difficulties and that required reconsideration of literature observations were modified with the agreement of the subgroup responsible for the corresponding topic. The new version of the synthesis document was then sent via e-mail to all panel members for their additional comments. Lingering disagreements were openly addressed and discussed in e-mails.

The recommendations were then subjected to a vote of approval via a poll conducted with the online tool SurveyMonkey®. Each item of a recommendation was evaluated on a 5-point Likert scale, ranging from "Strongly agree" to "Strongly disagree" and with a "Neutral" response at the midpoint. All members of the final panel had to vote, except for the 3 not involved in clinical care who could opt for a "No opinion" response. A minimal consensus threshold of 80% of the responses being "Strongly agree" or "Agree" was established to accept that consensus had been found; the "No opinion" responses were not counted in the denominator of the computations. The items for which the threshold was not reached or for which other questions were raised were subjected to a new vote after being rephrased. The agreement level of each recommendation was also expressed as a median (interquartile range [IQR]) calculated by weighting each response level by values ranging from 5 (for "Strongly agree") to 1 (for "Strongly disagree"). Higher medians indicated higher agreement levels and narrow IQR indicated higher consistency in the raters' judgments.

1.3. Publication procedure

All the work documents, including the synthesis document with the literature review summaries and recommendations, were written in French. The final version of the synthesis document was included in its entirety in the manuscript. After being approved by all the authors, the complete manuscript was translated by an experienced, native English-speaking biomedical translator and submitted for publication in English. After acceptance for publication of the English version, the modifications made in response to peer review comments were included in the French text for simultaneous publication of both versions.

2. Results

The development of recommendations lasted from February 2014 to May 2015. The topics selected and their respective objectives, given in Table 1, covered terminology (1 topic), nomenclature and classification (1 topic), diagnostic methods (6 topics) and treatment guidelines (7 topics). The literature summaries for each topic treated are given in the following sections, followed by a short commentary highlighting the panel's opinion on the interpretation of available information.

The panel's consensus recommendations are reported in Table 2. The 15 topics addressed resulted in 31 recommendations. All the recommendations reached 80% agreement and weighted agreement medians of 4 or 5 (Table 2, Fig. 2). The agreement level also reached 80% when the calculations were based on the responses for only the 26 senior panel members (data not shown).

2.1. Topic 1: terminology

GCA has been given several names. "Temporal arteritis" or "cranial arteritis" were extensively used to designate GCA but have fallen into disuse. "Horton's disease" is mainly used in Europe, especially in France, after the American neurologist who contributed to its description in 1932 [6]. GCA is the most-used term today, in almost 70% of the publications [7] and was adopted by the International Chapel Hill Consensus Conference Nomenclature of Vasculitides [8,9] and American College of Rheumatology (ACR) [10] classification of vasculitis.

Table 2
Recommendations retained for 15 topics concerning giant cell arteritis (GCA) management.

Item	Recommendation	Level of agreement[a]	
		Strongly agree or agree (%)	Median (IQR)
Topic 1: terminology			
1a	The term "giant cell arteritis" (GCA) or "giant cell arteritis (Horton's)" should be used	100	5 (0)
Topic 2: nomenclature and classification			
2a	GCA should be defined as arteritis of the aorta and/or its branches in a person > 50 years of age with cranial (clinical or histological) or ophthalmic involvement	93.8	5 (1)
2b	For research purposes, the American College of Rheumatology (ACR) classification criteria should be used to classify a vasculitis as GCA	96.9	5 (1)
Topic 3: clinical diagnosis			
3a	GCA diagnosis should be considered particularly in patients > 50 years of age with new-onset headaches, jaw claudication, abnormal temporal artery on physical examination or visual symptoms of sudden onset	100	5 (0)
3b	We do not advise determining a diagnosis of GCA with high certainty based on clinical findings alone and without performing additional diagnostic tests	96.8	5 (0.5)
Topic 4: temporal artery biopsy (TAB)			
4a	TAB should be obtained to determine the diagnosis of GCA with high certainty, but it should not delay treatment initiation, and a negative biopsy does not exclude the diagnosis	100	5 (0)
4b	TAB findings are compatible with GCA in the presence of mononuclear cell infiltrates of the media; additional findings of giant cells in the infiltrate and/or elastophagia can be considered highly specific for GCA	100	5 (1)
4c	First-line TAB strategy should be based on a unilateral biopsy, at least 1-cm long and examined in numerous serial sections	100	5 (0)
Topic 5: temporal artery imaging			
5a	Temporal artery imaging with Doppler ultrasonography or MRI cannot replace the TAB as the first-choice diagnostic examination	93.8	5 (1)
5b	Doppler ultrasonography of the temporal arteries must be performed by an experienced operator	100	5 (0)
5c	MRI of the temporal arteries is not recommended	93.9	4 (1)
Topic 6: imaging of the aorta and its branches to diagnose GCA			
6a	A clinical diagnosis of GCA can be supported by angio-CT, angio-MRI or ^{18}FDG-PET-scan demonstration of arteritis of the aorta or its branches, but imaging of the aorta and its branches cannot replace the TAB as the first-choice examination	93.9	5 (0)
Topic 7: biomarkers			
7a	Laboratory tests in the diagnostic work-up of GCA should include measurements of C-reactive protein and an inflammatory marker with slower response (erythrocyte sedimentation rate or fibrinogen)	100	5 (1)
7b	We do not recommend measuring biomarkers other than C-reactive protein, erythrocyte sedimentation rate and fibrinogen in the diagnostic work-up of GCA or for monitoring disease activity	96.8	5 (1)
Topic 8: search for aortic complications			
8a	CT or MRI screening for complications of aortitis is recommended at GCA diagnosis, then every 2–5 years, provided the patient has no contraindications to a potential aorta repair	93.8	5 (1)
Topic 9: glucocorticoid therapy of uncomplicated GCA (i.e., without ophthalmic involvement and without arteritis of the aorta or its branches)			
9a	We recommend treating uncomplicated GCA with oral prednisone at a starting dose of 0.7 mg/kg/day, then gradually tapering to reach 15–20 mg/day at 3 months, 7.5–10 mg/day at 6 months, 5 mg/day at 12 months and weaning off glucocorticoids within 18–24 months	100	5 (1)
9b	The systematic initiation of treatment with intravenous methylprednisolone pulse(s) is not recommended	100	5 (0)

Table 2 (*Continued*)

Item	Recommendation	Level of agreement[a]	
		Strongly agree or agree (%)	Median (IQR)
Topic 10: treatment of GCA with ophthalmic involvement			
10a	Suspected GCA with transient or permanent ophthalmic involvement should be treated immediately with 1 mg/kg/day of oral prednisone or 500–1000 mg/day of intravenous methylprednisolone for 1–3 days (followed by oral prednisone at 1 mg/kg/day), according to the regimen that can be most rapidly initiated	100	5 (0)
10b	The tapering schedule and duration of glucocorticoid treatment for GCA with ophthalmic involvement should follow the same regimen as that recommended for uncomplicated GCA	96.8	5 (1)
10c	Aspirin (75–300 mg/day) should be advised for GCA with ophthalmic involvement	96.8	5 (1)
Topic 11: treatment of GCA with aortoarteritis			
11a	GCA with uncomplicated and asymptomatic involvement of the aorta or its branches can be treated with the glucocorticoid regimen recommended for uncomplicated GCA	90.3	5 (1)
11b	For complicated (dilation, aortic aneurysm or dissection) or symptomatic (limb claudication or ischemia) aortoarteritis at GCA onset, oral prednisone at 1 mg/kg/day can be prescribed as a starting dose	87.1	4 (1)
11c	Except for emergency situations, repair of an aortic lesion should be scheduled once the systemic inflammatory response has subsided	93.8	5 (0)
Topic 12: adjunctive immunosuppressant or immunomodulatory treatment			
12a	The systematic prescription of an immunosuppressant or immunomodulatory agent for newly-diagnosed GCA is not recommended	100	5 (0)
12b	Adjunctive immunosuppression with methotrexate could be considered in selected patients with newly-diagnosed GCA for whom glucocorticoid-sparing is a major concern	87.1	4 (1)
Topic 13: targeted biologic therapies			
13a	Prescribing a targeted biologic therapy at GCA diagnosis is not recommended	93.5	5 (0)
Topic 14: aspirin, anticoagulants and statins			
14a	Low-dose aspirin (75–300 mg/day) should be considered for every patient with newly-diagnosed GCA upon benefit–risk assessment; for GCA with ophthalmic involvement, prescribing low-dose aspirin should be advised	100	5 (1)
14b	The systematic prescription of an anticoagulant or a statin is not recommended	93.5	4 (1)
Topic 15: treatment of relapse and recurrence			
15a	For a first relapse or recurrence, treatment with glucocorticoids is recommended at a dose that depends on symptom severity and by at least returning to the previously effective dose	100	5 (0)
15b	For multiple relapses or recurrences or patients with glucocorticoid-dependent GCA on 10–15 mg/day of prednisone (or an equivalent compound), adjunctive methotrexate can be prescribed; tocilizumab can be considered in case of methotrexate failure	93.5	4 (1)
15c	A purely biological "relapse" or "recurrence" does not necessarily require glucocorticoid dose intensification or the initiation of adjunctive therapy but should prompt closer monitoring	96.8	5 (1)

^{18}FDG-PET: ^{18}fluorodeoxyglucose positron-emission tomography; MRI: magnetic resonance imaging; CT: computed tomography.

[a] The level of agreement for each of the 31 recommendation items corresponds to the percentage of panel voters who indicated "Strongly agree" or "Agree" and the median (interquartile range [IQR]) calculated after weighting the evaluations by the voters among the Likert scale choices from 5 ("Strongly agree") to 1 ("Strongly disagree").

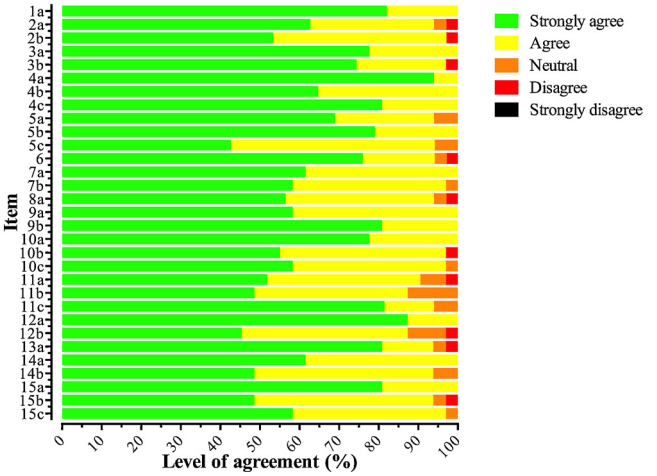

Fig. 2. Distribution of the levels of agreement among the 33 panel members for each of the 31 items (derived from the 15 topics) for which recommendations were formulated. The item numbers and their corresponding recommendations are fully developed in Table 2.

Comments: the term GCA is not limited to a histological finding but is a synonym of the anatomical-clinical entity "Horton's disease", including when TAB is negative for typical features of GCA. In the French literature, the term "giant cell arteritis (Horton)" can be used.

2.2. Topic 2: Nomenclature and classification

GCA is classified in the group of large-sized vessel vasculitides and defined as a disease affecting the aorta and its primary branches, with a predilection for external carotid and vertebral arteries [9]. Takayasu disease, sometimes considered to form a syndromic spectrum with GCA [11], is distinguished from GCA mainly by its onset before 50 years of age [9]. Polymyalgia rheumatica and isolated idiopathic aortitides can be differentiated from GCA by their absence of cranial (clinical or histological) and ophthalmic symptoms and signs. Demographic and clinical characteristics of isolated idiopathic aortitis in older adults differ from those of GCA [12], and the most recent International Chapel Hill Consensus Conference nomenclature considers it an entity distinct from GCA [9]. The ACR classification criteria for GCA require cranial manifestations (recent onset headaches, abnormal temporal artery on physical examination or positive TAB result). They enable GCA to be distinguished from another systemic vasculitis with 94% sensitivity and 91% specificity [10].

Comments: in the absence of documented vasculitis, classification of a disease as GCA is problematic. It can only be considered by including other information, such as the response to glucocorticoids and evaluation of the disease course during patient follow-up.

2.3. Topic 3: clinical diagnosis

Some clinical signs are highly suggestive of a diagnosis of GCA. The results of a large meta-analysis [13] suggested that claudication of the jaw (34% of the patients) and diplopia (9%) are the 2 clinical manifestations most strongly predictive of TAB-positive GCA (positive likelihood ratios: 4.2 and 3.4, respectively). Another study showed that headaches (86%), claudication of the jaw (42%) and temporal artery abnormalities on physical examination (44%) significantly increased the probability of TAB-positive GCA (relative risk: 3.6, 2.9 and 2.5, respectively) [14]. In the presence of polymyalgia rheumatica, the association of recent onset headaches, claudication of the jaw and a clinical temporal artery anomaly confer a positive predictive value of 97% and positive likelihood ratio of 47 to support a diagnosis of GCA; disease onset after 70 years of age increased the positive predictive value to 100%, but this association was seen in only 27% of the patients with polymyalgia rheumatica [15].

Comments: although not supported by study results, tongue [16] or scalp necrosis [17] and acute ischemic visual disorders are probably also strongly suggestive of GCA.

2.4. Topic 4: temporal artery biopsy

A diagnosis of GCA can be confirmed by a TAB. The association of an inflammatory infiltrate in the media with the presence of giant cells and elastophagia can be considered characteristic of GCA [18], but both of the latter features are not always found [19]. An isolated, inflammatory periadventitial infiltrate [20,21] or vasculitis (rarely necrotizing) of small vessels surrounding the temporal artery [21–23] is less common and can also indicate a temporal artery involvement of another systemic vasculitis [21,22,24].

The TAB is positive in 49%–85% of GCA patients [14,25–28]. These variations probably reflect differences in the clinical and histological definitions of GCA as well as technical differences in obtaining and processing the biopsy. The diagnostic yield seems maximal for biopsies of at least 0.5–1 cm [29–32] and increases somewhat with the multiplication of histological sections [20]. Compared to bilateral biopsies, a unilateral biopsy can identify 88% of the TAB-positive GCA cases [33]. The contribution of Doppler ultrasonography (US) to guide the site of TAB remains controversial [34–36]. Histological anomalies are detectable for at least 15 days after glucocorticoids are started [37,38]. TAB complications are rare [39].

Comments: no real consensus exists on the histological criteria defining GCA.

2.5. Topic 5: temporal artery imaging

Temporal artery imaging has been suggested as a valuable modality for confirming GCA. Color Doppler ultrasound (US) with high-resolution linear probes is the most studied technique. A hypoechogenic halo of the vessel wall [40] has 68% sensitivity (for GCA meeting ACR classification criteria) and 91% specificity [41]. Specificity increases when the halo sign is bilateral [41]. Sensitivity increases when halo signs of the axillary and common carotid arteries are also considered [42].

Magnetic resonance imaging (MRI), 1.5 Tesla (1.5 T) or 3 T, with gadolinium injection has been less studied. Vessel wall thickening with contrast medium uptake and lumen reduction are suggestive of the diagnosis [43]. The largest study, which considered temporal and occipital artery involvement, achieved 78% sensitivity and 90% specificity [44]. No significant difference in diagnostic yield has been found between Doppler US and 1.5 T or 3 T MRI [45]; 1 T MRI is not sufficiently sensitive [46].

Comments: imaging of the temporal artery does not support the GCA diagnosis with as much certainty as TAB. The practical value of Doppler US is difficult to assess because of the heterogeneous study findings and the high dependence on the operator for image acquisition. In France, Doppler US is little used and has yielded mixed results [47]. MRI, 1.5 T or 3 T, is even less well evaluated, is more expensive and less available than Doppler US.

2.6. Topic 6: imaging of the aorta and its branches to diagnose GCA

The detection of aortitis or arteritis of a branch of the aorta can lead to suspicion of GCA and contribute to its diagnosis.

The frequency of aortitis at GCA diagnosis has been most extensively evaluated by angio-computed tomography (CT) scans [48–52], angio-MRI [53–56], ^{18}fluorodeoxyglucose positron-emission tomography (^{18}FDG-PET) or ^{18}FDG-PET scan [49,53–55,57–59]. Aortitis is usually defined as regular circumferential wall thickening $\geq$ 2 or 3 mm on angio-CT images, wall gadolinium uptake on angio-MRI and homogeneous wall hypermetabolism on ^{18}FDG-PET images. Its frequency on angio-CT or angio-MRI ranges from 33% to 65% [48–55]. According to 2 meta-analyses, the sensitivity and specificity of PET demonstration of aortoarteritis at GCA diagnosis were 80% and 89% [60] and 90% and 98% [61], respectively. The results of a prospective study showed that the sensitivity of PET for detecting aortoarteritis was barely superior to that of MRI [53]. The authors of a recent retrospective study reported a greater ability of PET to detect inflammation of aorta branches than angio-CT [49]. Arterial Doppler US can reveal halo signs of the common carotid [42], axillary and iliac-femoral arteries [62,63].

Comments: literature findings are heterogeneous but indicated that imaging demonstration of aortoarteritis is less specific than TAB for GCA. Interpretation of imaging results remains difficult for aortic walls that are only moderately thickened, enhanced by contrast medium or hypermetabolic. Although PET could be more sensitive for visualizing aortoarteritis, the choice among angio-CT, angio-MRI and PET should be made case by case and by taking accessibility into account.

2.7. Topic 7: biomarkers

An erythrocyte sedimentation rate (ESR, Westergren) $\geq$ 50 mm/h is one of the ACR criteria for GCA classification [64]. Inflammatory marker levels are almost always increased during the initial phase of GCA, with a mean ESR of 93 mm/h and a mean C-reactive protein (CRP) level of 94 mg/L [65]. Levels of other inflammatory proteins (fibrinogen, haptoglobin, orosomucoid) may also be elevated. Anemia of inflammation is seen in 55% of patients, and 49% have thrombocytosis [65]. Nonetheless, 11% of the patients have ESR < 50 mm/h [66], and normal levels of inflammatory markers do not preclude a diagnosis of GCA [67]. An association between moderately increased inflammatory marker levels and ocular ischemic complications has been reported [68].

Anti-cardiolipin [69–73], anti-endothelial cell [74,75] or anti-human ferritin heavy chain antibodies [76,77] have been detected during the course of GCA. Serum pentraxin-3 level is also elevated in GCA [78]. A contribution to GCA diagnosis has not been demonstrated for these biomarkers.

Comments: at present, there are no known specific biomarkers for the diagnosis of GCA or for determining distinct disease phenotypes or prognoses.

2.8. Topic 8: search for aortic complications

The aortic aneurysm rate is higher for GCA patients than the general population [79,80], especially in the ascending thoracic aorta (relative risk 17) [79]. According to cohort studies, the aortic aneurysm and/or dissection incidence was 19/1000 person-years [81,82]. An aneurysm can be discovered several years after GCA diagnosis by an aortic dissection or rupture [79], but in 15% of patients with aortitis, a thoracic aorta aneurysm or dilatation is present at GCA diagnosis [52]. Aortic aneurysm or dissection following the diagnosis of GCA are associated with shortened survival [83].

Comments: there are no known factors that can predict an aortic complication. The screening modalities (type of imaging, periodicity) for aortic complications are not well defined. For CT and MRI, contrast media is not required for analysis of the caliber of the aorta but does enable evaluation of the vessel wall and lumen. Conventional chest radiography has mediocre sensitivity to detect an aortic abnormality [84].

2.9. Topic 9: glucocorticoids to treat uncomplicated GCA (i.e., without ophthalmic involvement and without arteritis of the aorta or its branches)

Glucocorticoids are the historical gold standard for treatment of GCA. The initial dose for uncomplicated GCA ranges from 0.3 mg/kg/day [85,86] to 1 mg/kg/day of prednisone or another equivalent compound [87]. The results of some studies indicate that 0.5–0.7 mg/kg/day is usually adequate to control the disease and is well tolerated [85,86,88,89]. A randomized clinical trial showed that 3 consecutive daily intravenous methylprednisolone pulses (15 mg/kg/day) before oral glucocorticoids was beneficial in reducing relapse rates and had an oral glucocorticoid sparing effect [90]. Prednisone has less inter-individual variability of plasma concentrations than prednisolone [91].

The initial dose is maintained for 2–4 weeks, depending on how quickly the inflammatory syndrome subsides [92,93]. Glucocorticoid tapering starts quickly to reach 0.2–0.3 mg/kg (15–20 mg/day) in 6–10 weeks [94]. Prospective and retrospective studies have shown that about half of patients achieve a dose of 0.13 mg/kg (7.5–10 mg/day) by 6 months [89,93]. Conversely, withdrawal of steroids at 6 months of treatment in patients enrolled in a controlled clinical trial resulted in a 77% relapse rate at 1 year of follow-up [92]. Median treatment duration lasted about 24 months in observational cohort studies with a wide range, often many years [88,95].

Comments: no international consensus has been reached for the initial glucocorticoid dose for uncomplicated GCA. The administration of methylprednisolone pulses to older patients or those with comorbidities can be problematic.

2.10. Topic 10: treatment of GCA with ophthalmic involvement

Ophthalmic involvement is the most common severe GCA complication, with 13%–19% of patients experiencing irreversible ischemic injuries due to occlusion of ophthalmic artery branches [25,96–99] or, more rarely, posterior occipital artery strokes [96,100]. Visual acuity of the affected eye is < 20/200 for most patients [101,102] and ophthalmic involvement occurs in both eyes in one third. In 95% of the patients, visual impairment occurs before starting glucocorticoids [96,99,103], with a mean interval of 6 weeks after the first symptoms [96,103,104]. In about 20% of patients, ophthalmic involvement is the initial manifestation [96,101,102]. A few patients starting glucocorticoids within 72 hours may achieve partial visual improvement [105–107]. Ipsilateral deterioration or contralateral amaurosis occurs in about 10% of patients during the first days of therapy [96,102,108].

The best therapeutic results were obtained with oral prednisone (or its equivalent) of at least 60 mg/day [96,106,107,109] or 500 mg of intravenous methylprednisolone [105–107,109]. The findings of 2 retrospective studies suggested that low-dose aspirin prevented ocular and cerebral ischemic complications [98,110]. The potential role of anticoagulants has not been adequately investigated [111].

Comments: we lack prospective study or controlled clinical trial results to guide glucocorticoid regimens or use of low-dose aspirin for GCA with ophthalmic involvement.

2.11. Topic 11: treatment of GCA with aortoarteritis

Arteritis of the aorta or its branches can be complicated by dilation, aneurysm or dissection of the aorta and stenosis or occlusion of a large branch of the aorta. Such complications raise the question of

specific therapeutic measures, but no retrospective or prospective study has compared different glucocorticoid regimens or evaluated glucocorticoid-sparing treatments for GCA with aortoarteritis. Aortitis [112] or involvement of subclavian arteries [113], regardless of the severity, could be associated with increased risk of relapse, glucocorticoid dependency and cardiovascular mortality [112,113] but remains controversial [114]. Aortic aneurysm or dissection (but not stenosis of a large branch of the aorta) is associated with increased cardiovascular mortality [83]. Prednisone (or an equivalent compound) at 1 mg/kg/day is prescribed empirically for GCA with signs of limb ischemia [115]. Endovascular treatment or surgery for an aortic aneurysm follow the same treatment principles as those applied for situations not linked to GCA. Acute aortic dissection is a surgical emergency.

Comments: whether GCA with uncomplicated and asymptomatic aortoarteritis requires more intensive medical therapy remains an open question.

2.12. Topic 12: adjunctive immunosuppressant or immunomodulatory therapy

The addition of immunosuppressive or immunomodulatory agents to the therapeutic regimen to achieve glucocorticoid-sparing or to prevent relapse in GCA patients has been investigated. Adjunctive methotrexate was examined in 3 randomized placebo-controlled clinical trials [87,92,116], a meta-analysis of individual patient data [117] and another meta-analysis of aggregated data [118]. According to the meta-analysis of individual data, oral methotrexate at 7.5–15 mg/week at diagnosis lowered the risk of relapse and the cumulative glucocorticoid dose [117].

Other immunosuppressants or immunomodulators were evaluated during GCA, with negative or less robust results. Adjunctive azathioprine (150 mg/day) was assessed in an early randomized placebo-controlled trial conducted on a small sample of patients with GCA or polymyalgia rheumatica. The results showed a glucocorticoid-sparing effect of azathioprine at month 12 of follow-up [119]. Randomized clinical trials of adjunctive therapy with cyclosporine [120], hydroxychloroquine [121] or dapsone [122] found either no efficacy [120,121] or tolerance problems [121,122]. Uncontrolled retrospective studies reported the beneficial effects of cyclophosphamide [123–125], leflunomide [126,127] or mycophenolate mofetil [128] on control of GCA.

Comments: at present, we have insufficient evidence to advocate the use of an adjunctive immunosuppressive or immunomodulatory agent other than methotrexate. The efficacy of methotrexate seems modest.

2.13. Topic 13: targeted biologic therapies

The advent of targeted biologic therapies raised the question of their potential benefit in GCA treatment to prevent relapse or reduce glucocorticoid exposure. Data from prospective studies on the use of biologic drugs at GCA diagnosis as glucocorticoid-sparing agents are available for only anti-tumor necrosis factor-alpha (TNF-α). Three randomized trials evaluating infliximab, etanercept or adalimumab did not show any benefit for the primary endpoints [93,129,130]; the smallest of those trials found an etanercept effect on a secondary endpoint with a statistically significant reduction of cumulative glucocorticoid doses after 12 months of treatment [130].

The only available information for other biologic therapies is from uncontrolled studies examining patients with relapsing or refractory GCA, generally after the use of methotrexate. Tocilizumab is currently the most promising biologic therapy. It markedly reduces inflammatory biomarkers and appears very encouraging for clinical and imaging outcome measures [131–142]. The efficacy of anakinra or rituximab was reported for 3 [143] and 2 patients with GCA [144,145], respectively.

Comments: the side effects of tocilizumab (notably infectious, hematological, hepatic and gastrointestinal) and the current lack of robust evidence of efficacy should prompt caution while awaiting the results of an ongoing international randomized placebo-controlled clinical trial of this agent for management of GCA [146].

2.14. Topic 14: aspirin, anticoagulants and statins

For GCA patients, the increased short-term risk of ocular, cerebral and cardiovascular ischemic events [99,147] and increased intermediate- and long-term risk of cardiovascular and cerebral ischemic events [100,147–149] raise the question of measures conferring vascular protection. For GCA patients taking glucocorticoids, the results of several cohort and retrospective studies [98,110,150] and a meta-analysis of retrospective studies [151] suggested that low-dose aspirin ($\leq$ 100 mg/day), given for primary [98] or secondary prophylaxis [151], diminished the risk of cerebral or ocular ischemic attacks and the risk of cardiovascular events in general. Another retrospective study indicated the protective effect of low-dose aspirin on risk of relapse [152]. The possible benefit of anticoagulants is poorly documented [110]. The effect of statins on the risk of cardiovascular complications during GCA has not been evaluated. The findings of 3 retrospective cohort studies [153–155] showed no advantage of statin use in terms of glucocorticoid sparing effect, whereas an observational population-based study suggested a benefit of statins on reducing the duration of glucocorticoid use [156].

Comments: as a matter of principle, prophylactic low-dose aspirin or statin use should follow the current recommendations for preventing complications of atherosclerosis.

2.15. Topic 15: treatment of relapse and recurrence

At least one third of patients experience clinical–biological relapse or recurrence of GCA previously in treatment-induced remission [157,158]. Some authors distinguish between relapse that appears under treatment and recurrence that occurs at some time after stopping glucocorticoids. The isolated reappearance of increased inflammatory marker levels is usually not sufficient to diagnose a relapse.

No controlled trial has been conducted to guide the treatment choices for GCA relapse or recurrence. The results of a meta-analysis of data from patients with newly-diagnosed GCA who participated in 3 randomized placebo-controlled clinical trials indicated that methotrexate significantly lowered the risk of 2 consecutive relapses [117]. The usefulness of cyclophosphamide [123–125], leflunomide [126,127], mycophenolate mofetil [128] or tocilizumab [131–141] to treat high-dose glucocorticoid-dependent GCA or GCA with multiple relapses was suggested by uncontrolled studies usually involving small patient samples.

Comments: the management of GCA relapse and recurrence is poorly defined, and whether adjunctive therapy should be initiated in such situations remains debated.

3. Discussion

The recommendations elaborated herein addressed 15 topics, mostly referring to diagnostic and therapeutic aspects, for which we perceived a need for harmonizing the standards of GCA management. Although the panel was essentially composed of university hospital physicians, these recommendations are also intended for management of patients with GCA seen in non-teaching hospitals and private practice. Except for possible differences across

nations in healthcare systems or access to medications, these recommendations should also be applicable in countries outside of France.

Our recommendations should be viewed as the result of group consensus, defined as approval by at least 80% of the voters and they do not necessarily reach unanimity among people outside our panel. The results of original studies are prone to divergent interpretations, and several of our choices relied on clinical experience criteria. The fact that most of the panel members were internists raises the question of the generalizability of these recommendations to patients seen by other medical specialists. However, in France, internal medicine is a primary-care specialty which cares for patients suspected of having GCA, and we believe that our panel of 33 participants could offer comprehensive expertise on the various situations practitioners may encounter when caring for patients with GCA.

We decided not to score the level of evidence or grade our recommendations as "strong" or "weak" [159]. For a rare disease, the scarcity of original high-quality studies and the small number of patients included in them means that the quality of evidence is limited and thus provide little basis for this type of ranked evaluation. Moreover, such notations are poorly applicable to older drugs, such as glucocorticoids, for which no proof of efficacy was ever provided by a randomized clinical trial, or to the evaluation of diagnostic tests [160]. By contrast, we have highlighted the reasoning that has led to our recommendations in the commentaries accompanying the literature syntheses, and we reflected uncertainties about given recommendations in the prudent phrasing we have chosen. Our degree of confidence in each of the recommendations is reflected by the levels of agreement, usually elevated, obtained during the validation process.

The topics dealing with the diagnosis and treatment of GCA involving the aorta and its branches stirred fierce discussions in the process of reaching consensus. That debate reflects our current insufficient knowledge of the best modalities to assess for involvement of the aorta or its branches and the prognostic and therapeutic implications of such manifestations. We also debated whether people > 50 years old diagnosed with isolated idiopathic aortitides should be considered as having GCA. The agreement adopted by our group stipulates that cranial or ophthalmic manifestations must be present for a GCA diagnosis. As a consequence, these therapeutic recommendations are not implicitly applicable to isolated idiopathic aortitides. A better understanding of the relationships between GCA and the other idiopathic aortitis forms and of GCA subsets with distinct prognostic profiles represents a major future research need.

The results of this work are only partially comparable to recommendations published under the aegis of the British Society of Rheumatology (BSR) [161] or the European League Against Rheumatism (EULAR) [162]. Our position on TAB as a first-choice diagnostic tool, as opposed to temporal or large-vessel imaging, is in agreement with BSR and EULAR recommendations. In contrast, our recommendation concerning the indications for prescribing adjunctive immunosuppressant therapy, especially methotrexate, is more conservative than that from the EULAR, which advises first-line methotrexate to treat GCA. A significant contribution of our effort is that it devised recommendations for difficult practical questions, such as treating GCA with aortoarteritis or the role of targeted biologic agents to treat relapses.

In conclusion, these recommendations provide many practical suggestions for GCA management. They will be expanded and require updating as new data become available, which will lead to changing the way we define, classify, diagnose and treat GCA. In the future, the medical–economic characteristics of different diagnostic or therapeutic strategies, not addressed here because of our lack of information, will also need to be considered.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.revmed.2015.12.015.

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