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INVITED REVIEW

Management of Giant Cell Arteritis

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Giant cell arteritis (GCA) is the most common primary vasculitis in people aged 50 years and older. Although there are names such as Horton's disease and temporal arteritis among the first names of the disease, GCA; is evaluated in two groups as cranial giant cell arteritis and large vessel giant cell arteritis [1]. Polymyalgia rheumatica may accompany both subtypes (Figure 1). There may be differences in subgroups between countries and clinics. Distribution of patients from France and Turkey is shown in Figure 1 [2].

In recent years, the concept of disease management is used for many chronic diseases such as diabetes mellitus, asthma. In this review, we prefer to use the disease management strategy to indicate multiple steps of patient care of GCA.

When the treatment strategy is planned, at the time the evaluation of the patient is completed, the patient and their relatives should be informed about the disease and prognosis. Furthermore, their views and expectations about the disease also should be taken into account during the decision of medical treatments. The web page of our vasculitis center can be visited for patient information recommendations http://www.vaskulit.hacettepe.edu.tr/hastalar.shtml [3].
It is very important to prevent our patients from obtaining information from unsafe sources. Additionally, since there is not enough information about the use of herbal products, the use of these products is not recommended in terms of possible side effects.

Multidisciplinary approach and Fast-track clinics in GCA

As in many rheumatological diseases and different types of vasculitis, multidisciplinary collaboration is vital in the differential diagnosis of patients suspected of GCA; not only for the evaluation of symptoms and signs, but also for follow-up of treatment efficacy and adverse events. Rheumatology, Ophthalmology, Neurology, and Internal Medicine clinics are the main clinics that patients frequently apply first. Due to the fact that constitutional symptoms such as weight loss and fever can be evident, the opinions of the infectious diseases and medical oncology departments of the patients can be obtained, especially during the first presentation periods.

Radiology (Doppler Ultrasonography of the temporal and axillary arteries, Computerized tomography/Magnetic resonance imaging angiography of the great vessels, and Nuclear Medicine (Positron Emission Tomography) help in the diagnosis and understanding the extent of the disease. Additionally, interventional angiography is helpful in case of indication. Evaluation of temporal artery biopsy samples taken by neurosurgery or plastic surgery departments is the current standard approach.

Several strategies have been introduced to reduce the rate of morbidity mainly from sudden vision loss. Fast-track clinic gives opportunity for a multidisciplinary approach. Using temporal artery US and confirmation by biopsy as a fast-track clinic is related to better prognosis [4].

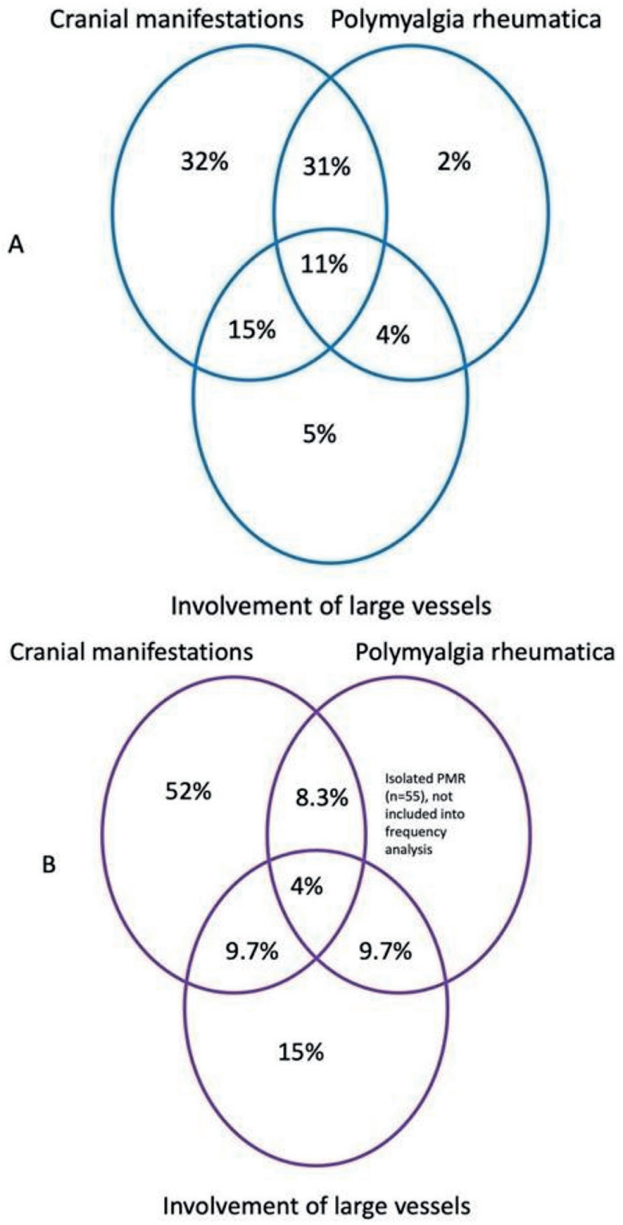

Figure 1. The distribution of GCA subtypes in Artemis study (n=360) (A) and Hacettepe Vasculitis Prospective Database (n=72) (B)

We established our fast-track clinic including radiology, ophthalmology, surgeons, and pathology departments and rheumatology as the team leader at Hacettepe University Vasculitis Center in 2016 and still have been working as a collaborative team.

Detailed evaluation of patients with suspected diagnosis of GCA

The distribution and severity of the disease should be clearly defined using a systemic approach. Questioning the patient regarding the symptoms and performing optimal physical examination using a checklist is recommended which is being done at Hacettepe University Vasculitis Center (Table 1) [3].

Table 1. Visit checklist including signs and symptoms of GCA [6]

Constitutional	Fever >38° C
	Fatigue
	Unintentional weight loss
Neurologic	Transient ischemic attacks
	Syncope
	Cerebrovascular accident
	New/worse headache
	Hemiparesis/paraparesis
Ocular	Amarozis fugax
	Blurred vision
	Retinal vasculitis (thrombosis or aneurysm)
	Sudden vision loss
	Scotom/diplopia
Cutaneous	Scalp tenderness/necrosis in scalp
Musculoskeletal	Arthralgia
	Myalgia
	Morning stiffness
	Shoulder/neck/hip pain
Cardiovascular	Carotidynia
	Chest pain, pericardial or angina
	New onset hypertension
	Other symptoms related to vascular insufficiency
Gastrointestinal	Abdominal pain (vasculitis)
Vascular parameters	New murmurs
	New loss of pulses
	New weak pulses
	Asymmetric blood pressure
	Pulse discordance
	Extremity claudication
	Increase in blood pressure
Laboratory abnormalities	Erythrocyte sedimentation rate
	C-reactive protein
	Hemoglobin/Hematocrit
Patient based assessments	General health measures
	SF-36
	Pain Visual analogue scale (VAS, 0-100)
Clinician based assessments	Physician global scale (0-100)
	Relapse
	Vascular Damage Index
	Increase in glucocorticoid dose
	New/increased immunosuppressive treatment

EULAR definitions of active disease, remission, relapse and refractory disease for GCA

Recommendations of national/international organizations should be taken into account in ensuring homogenization in disease activity assessments and reviewing treatment responses. Definitions for disease activity/damage such as flare, remission, sustained remission could be a part of routine daily practice in patients with GCA. Additionally, these definitions are helpful for better understanding of the literature. In this context, the criteria developed under the leadership of EULAR are frequently used and recommended by our center [5].

According to EULAR definitions [5] active disease, is defined as the presence of typical signs/ symptoms of active LVV and at least one additional item from;

i. Current disease activity on imaging/ biopsy.
ii. Ischaemic complications that are linked to LVV.
iii. Persistently elevated inflammatory markers not attributed to other causes

Remission state is defined as no sign/symptoms and normal acute -phase reactants under standard therapy. If the remission state is achieved for 6 months and individual target doses were reached, it is possible to mention from **sustained remission** and when all the glucocorticoids were stopped in this scenario, then it is called as **glucocorticoid-free remission**.

Instead of flare, **relapse** is the preferred term and divided into two: major and minor relapse. Recurrence of active disease with either clinical features of ischaemia or evidence of active aortic inflammation (causing aortic or large vessel dilatation, stenosis or dissection) is accepted as major relapse. If there is disease recurrence without fulfilling major relapse criteria, then it is called minor relapse. In a minority of patients, it is not possible to reach a remission state under standard therapy; it is called refractory disease.

Medical Treatments

Randomized studies are not feasible given that the GCA is rare in terms of medical treatments especially in the acute phase. Just after the diagnosis, high dose glucocorticoid (GC) therapy equivalent to 40–60 mg/day prednisolone is suggested for remission induction. A tapering strategy is also suggested when the disease is under control to a target dose of 15–20 mg/day within 2–3 months. Targeting a dose of≤5 mg/day after 1 year is suggested.

Patients with sudden vision loss are suggested to be treated by IV 1000 mg methylprednisolone for 3 days with tapering with oral treatment. GC treatment is necessary for both to prevent irreversible vision loss and all ischemic complications and to protect the other eye.

Even EULAR recommends the use of corticosteroids as solo, relapse is observed in 49-68% of patients during steroid tapering [6]. Thus, our vasculitis centre's approach is generally use of any conventional DMARD as a steroid-sparing agent [2].

Treatment can be tailored according to subphenotypes and responses might change among them. For example, de Boysson et al. showed that there is a significantly higher GC dependence in symptomatic large vessel GCA subgroup [7].

In Artemis study, 90/306 patients had at least one adjunctive treatment [8]. Hacettepe University Vasculitis Center results also showed that 87.5% of the patients had at least one adjunct treatment. In both cohorts, MTX is the most common agent used.

In a meta-analysis of 3 randomized placebo-controlled trials adjunctive MTX (7.5–15 mg/week) reduces the risk of first relapse by 35% and the risk of second relapse by 51%. In addition, this regimen had a steroid sparing effect more prominent in 24 months compared to 12 month [9].

In an-open label study, Hocevar et al. investigated the steroid sparing role of leflunomide 10 mg in GCA [10].Relapse was observed in 4 (13.3%) of leflunomide group vs. 18 (39.1%) of steroid-only group (p=0.02). Number needed to treat was found as 3.9. Further data is required to better understanding of the place of conventional DMARDS in GCA.

In refractory/ relapsing cases or when there is or an increased risk for GC side effects, adjunctive treatment with methotrexate (MTX) or tocilizumab (TOC) as an alternative were recommended.

IL-6 is a key mediator in the pathogenesis of GCA and PMR. Treatment with TOC was proven to induce prompt clinical, serologic, and radiologic

improvement in refractory/relapsing disease [11]. In Phase 2 study 85% patients in the tocilizumab group and 20% in the placebo group reached a relapse-free survival by week 52 (p=0·0010) with a cumulative prednisolone dose difference of 67 mg/kg (p=0·0005) after 52 weeks [12].

After Phase III study, TOC was approved as steroid sparing agent in GCA [13]. This study showed that 1862 mg of cumulative median dose of tocilizumab in each group, as compared with 3296/3818 mg in the placebo group that underwent the 26 and 52-week taper, respectively (P<0.001 for both comparisons).

Current approach in Turkey provides the use of TOC in patients resistant to csDMARDs after application to Ministry of Health to get approval for the usage.

Several points should be kept in mind before starting TOC, as acute-phase reactants will not be a disease marker anymore. There is a perforation risk particularly in cases with diverticuli (can be seen commonly in old population). Even additional cardiovascular burden is not proven, fasting cholesterol levels increases with the treatment. After 4-8 weeks of initiation, a control is suggested to understand any side effects and disease activity in short-term and then 6-month interval controls is recommended.

However, there are still some questions to be answered such as how long the treatment should be given [11]. Another point is, there are several reports of presence of biopsy proven arteritis in cases with clinically controlled disease raising suspicion of uncontrolled disease status in patients with palliated symptoms [11].

There are several other biologic agents in the pipeline with promising results such as abatacept, ustekinumab, updacitinib [14]. However, TNF-inhibitors do not seem to be efficacious in GCA. A case series reported the results of anakinra in 6 patients and showed steroid-sparing effect in refractory GCA [15].

Antiplatelet or anticoagulant therapy is not recommended routinely when there is no other indication such as cardiovascular disorders. However, it is suggested to considered individually for the cases with high risk of ischemic complications.

Elective vascular interventions were recommended to be left when a remission state is stable. However, in urgent situations such as arterial vessel dissection or life/organ threatening vascular ischaemia immediate referral to the vascular team is suggested.

Comorbidities

Life-style modifications to reduce cardiovascular risk and complications related to the treatment are prerequisites.

It should be noted that patients might have concomitant diabetes, hypertension, osteoporosis; It should be reminded that age-specific malignancy screening should be done. If necessary, the opinions of the Endocrinology department should be sought, as the drug treatments to be started may aggravate the accompanying diseases.

Relapse and Prognosis

Patients with major relapse was recommended to either initiate or increase the dose of GC therapy as recommended for new onset disease. In case of minor relapses an increase in GC dose at least to the last effective dose was suggested.

Mortality

A recent report, showed an increased all-cause mortality particularly occurring within the first year of diagnosis. Glucocorticoid-related complications are mostly responsible from the deaths [16].

Conflict of interest

Dr. Karadag received research grants from Novartis, Roche, Viela-Bio and a member of advisory Board, speaker of educational programmes for Amgen, Celltrion, Farmanova, UCB-Pharma.

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