LETTER TO THE EDITOR

Definition, aims, and implementation of GA²LEN/HAEi Angioedema Centers of Reference and Excellence

To the Editor,

GA²LEN, the Global Allergy and Asthma European Network, and HAE international (HAEi), the global umbrella organization for the world’s hereditary angioedema (HAE) patient groups, have launched their joint ACARE (Angioedema Center of Reference and Excellence) program, within GA²LEN’s center of reference and excellence (CORE) initiative. Angioedema is a common, heterogeneous, often debilitating and chronic condition and is frequently a challenge for physicians and affected patients, especially patients suffering from recurrent attacks. Additionally, it can be a challenge for some patients to understand the underlying etiology of their angioedema (Table 1). GA²LEN’s CORE networks, such as UCARE for urticaria and ADCARE for atopic dermatitis, help to improve the management of difficult-to-treat conditions. Here, we describe the aims, requirements, provisions, application process, audit, and accreditation protocol for GA²LEN/HAEi ACAREs. ACAREs aim to provide excellence in angioedema management, increase the knowledge of angioedema through research and education, and promote advocacy activities that raise angioedema awareness. To become a certified ACARE, angioedema centers must fulfill 32 requirements, defined by specific provisions that will be assessed during an audit visit. The ACARE program will result in a strong network of angioedema specialists, promote angioedema research and awareness, and harmonize and improve angioedema management globally. ACAREs will expand access to modern angioedema medicines in countries where they are available and help to bring them to countries where they are not.1

This document summarizes the aims of GA²LEN/HAEi Angioedema Centers of Reference and Excellence (ACAREs) and elaborates the requirements that ACAREs must fulfill to become certified. It also provides (see Appendix S1) background information on GA²LEN and HAEi, including HAEi member organizations and regional patient advocates, on why we need an Angioedema Center of Reference and Excellence (ACARE) program and network, and on the accreditation and certification process, governance and funding, and on the interaction with other GA²LEN networks of centers of reference and excellence. The protocols, aims, requirements, and provisions related to becoming a certified ACARE are based on (a) the experience of the GA²LEN UCARE network and (b) input from angioedema patients, general practitioners, and angioedema specialists.

What are the aims of GA²LEN/HAEi ACAREs? The aims of ACAREs are to set the global standard for excellence in comprehensive angioedema care through research, education, advocacy, and interaction among ACAREs. By serving as referral centers for the diagnosis and management of patients with angioedema, ACAREs will complement the local healthcare system. ACAREs aim to increase knowledge and awareness of angioedema.

TABLE 1 Classification of angioedema

| Bradykinin-mediated angioedema | Mast cell mediator-mediated angioedema | Unknown mediator |
|--------------------------------|--------------------------------------|-----------------|
| **C1-INH deficiency/defect** | **IgE mediated** | **Non-IgE mediated** | **Idiopathic AE** |
| Inherited | Acquired | Inherited | Acquired | Angioedema with or without wheals in patients with urticaria | Angioedema with or without wheals in patients with urticaria | Anaphylaxis |
| HAE-1 | AAEC1-INH | HAE nC1-INH (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-KNG1, HAE-UNK) | AE due to medication that interferes with BK degradation, eg ACEI | Angioedema with or without wheals in patients with urticaria | Angioedema with or without wheals in patients with urticaria |
| HAE-2 | HAE-C1-INH | | | |

Abbreviations: AAE-C1-INH, acquired angioedema due to C1-inhibitor deficiency; ACEI-AE, angiotensin-converting enzyme inhibitor-induced angioedema; BK, bradykinin; HAE nC1-INH, hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in factor XII (F12), angiotenopetin-1 (ANGPT1), plasminogen (PLG), kinogen-1 (KNG1), or unknown (UNK) (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-KNG1, HAE-UNK); HAE-1, hereditary angioedema due to C1-inhibitor deficiency; HAE-2, hereditary angioedema due to C1-inhibitor dysfunction.

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LETTER TO THE EDITOR

What are the requirements for GA²LEN/HAEi ACAREs? ACAREs are required to demonstrate excellence in the management of angioedema, research activities, efforts in education, and advocacy activity. ACAREs need to fulfill 32 requirements, which are explained in the audit checklist (Figure 1A). This checklist includes specific deliverables for each requirement. For example, the requirement to know and follow international guidelines and consensus documents for angioedema (Requirement #16) entails that physicians and other ACARE healthcare professionals have read and understood the current versions of these guidelines and consensus documents and that their recommendations are implemented in their center.

These guidelines and consensus documents include, for example, the international WAO/EAACI guideline for HAE, the EAACI/GA²LEN/EDF/WAO guideline for urticaria, the International/Canadian hereditary angioedema guideline, the international consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency, the international consensus on the use of genetics in the management of HAE, and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. The deliverables for this requirement are that (a) current guideline and consensus document versions are present (paper or electronic version) at the center, (b) ACARE staff can answer questions on the recommendations these documents provide, and (c) ACARE physicians can show, upon request, by use of a patient file, that patient management decisions are based on guideline recommendations (Figure 1B).

This publication marks our intent to start the implementation of the GA²LEN/HAEi ACARE initiative. Specialty centers for angioedema have started to apply to become ACAREs, and audits and certifications are ongoing (Figure 1B). We expect that most GA²LEN UCARE centers and many angioedema specialty centers will become ACAREs in the near future. We predict and hope that by 2022, GA²LEN/HAEi ACAREs will be established in every continent. This will result in a strong global network of angioedema specialists, promote angioedema research, and harmonize and improve angioedema management worldwide. GA²LEN and HAEi will measure the impact of ACAREs over time and document and report the benefits of this initiative. ACARE network activities and a current list of ACAREs are posted on the network’s website (www.acare-network.com).

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Additional supporting information may be found online in the Supporting Information section.