

# Consensus on the Definition of Control and Remission in Chronic Urticaria

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## ■ Abstract

The terms control and remission and other key terms used in chronic urticaria (CU) such as *flare-up*, *relapse*, *exacerbation*, and *recurrence* have not been fully defined in the literature. Disease monitoring and treatment goals in clinical practice are not well established. After a qualitative appraisal of available evidence, we aimed to find a consensus definition of control and remission, clarify key terminology, provide guidance on how to monitor the disease, and establish treatment goals in clinical practice. A modified Delphi consensus approach was used. Based on a literature review, a scientific committee provided 137 statements addressing controversial definitions and terms, available patient-reported outcomes (PROs), and recommendations on how to measure therapeutic objectives in CU. The questionnaire was evaluated by 138 expert allergists and dermatologists. A consensus was reached on 105 out of the 137 proposed items (76.6%). The experts agreed that complete control and remission of CU could be defined as the absence of signs or symptoms while on treatment and in the absence of treatment, respectively. Consensus was not reached on the definition of other key terms such as flare-up, exacerbation, and recurrence. The panel agreed that the objective of therapy in CU should be to achieve complete control. PROs that define the degree of control (complete, good, partial, or absence) were established. An algorithm for disease assessment is provided. In conclusion, this work offers consensus definitions and tools that may be useful in the management of patients with CU.

**Key words:** Chronic urticaria. Terminology as topic. Patient outcome assessment. Recurrence. Consensus.

## ■ Resumen

El concepto de control y remisión de la enfermedad, así como otros términos clave utilizados en la urticaria crónica (UC), como reanudación, recaída, exacerbación o recurrencia, no están totalmente aclarados en la literatura. Tampoco está bien establecido el seguimiento de la enfermedad y los objetivos del tratamiento en la práctica clínica. Tras una evaluación cualitativa de la evidencia, nos propusimos encontrar una definición consensuada de control y remisión de la UC, aclarar terminología clave, proporcionar orientación sobre cómo monitorizar la enfermedad y establecer objetivos de tratamiento en la práctica clínica. Para llegar a un consenso, se utilizó una técnica Delphi modificada. Basándose en una revisión de la literatura, un comité científico elaboró 137 aseveraciones que abordaban definiciones y términos controvertidos, el uso de *Patient Reported Outcomes* (PROs) y recomendaciones sobre cómo medir los objetivos terapéuticos en la UC. El cuestionario fue evaluado por 138 alergólogos y dermatólogos expertos. Se alcanzó un consenso en 105 de las 137 aseveraciones propuestas (76,6%). Los expertos estuvieron de acuerdo en que el control completo y la remisión de la CU podrían definirse como la ausencia de signos o síntomas de la enfermedad mientras se está en tratamiento y en ausencia de tratamiento, respectivamente. No se alcanzó un consenso sobre la definición de otros términos clave como reanudación, exacerbación o recurrencia. El panel estuvo de acuerdo en que el objetivo terapéutico de la CU debe ser lograr un control completo. Se establecieron los PROs que definen el grado de control de la CU (completo, bueno, parcial o ausencia de control). Además, se creó un algoritmo para la evaluación de la enfermedad. En conclusión, este trabajo ofrece definiciones y herramientas de consenso que pueden ser útiles en el manejo de los pacientes con CU.

**Palabras clave:** Urticaria crónica. Terminología como asunto. Evaluación del resultado de la atención al paciente. Recurrencia. Consenso.

## Introduction

Chronic urticaria (CU) is a common condition that markedly affects functioning and subjective well-being and entails considerable costs for both patients and the health system [1]. The point prevalence of CU, which is based on coding reports in health systems from different countries, ranges from 0.1% to around 1% globally [2]. CU affects mostly young and middle-aged women and usually lasts for several years (more than 1 year in 25%-75% of patients) [3]. Often, more than 1 year is needed before effective management is implemented [3].

The EAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines cover the definition and classification of urticaria [1]. However, the concepts of disease control and remission have not been fully clarified by these and other guidelines [4-8], and different definitions can be found in the literature [1,9-11]. While other key terms, such as flare-up, relapse, exacerbation, and recurrence, are commonly used in the literature and in clinical practice, there are no uniform criteria on their exact meaning and to what extent they are interchangeable [12-15]. In addition, guidelines provide recommendations on the use of patient-reported outcomes (PROs), but no precise recommendations are given on the cut-off points that should guide modifications to treatment [1,4-8,16-18].

In this work, we aimed to find a consensus definition of control and remission in CU and clarify key terminology related to relapse or recurrence. Additionally, we aimed to provide guidance on how to monitor the disease and on how to optimize the use of PROs in the decision-making process during the clinical management of patients with CU.

## Material and Methods

This project was based on a qualitative appraisal of available scientific evidence and a consensus method (modified Delphi) [19]. A scientific committee consisting of 10 experts with recognized experience in the management of urticaria was formed to lead the project. Details of the modified Delphi methodology used to reach consensus are shown in Table S1. In summary, after an exhaustive review of the literature and discussion, the scientific committee generated 137 debatable statements/items addressing the concept of control in CU and recommendations on how to monitor disease activity and its impact. The questionnaire was assessed online by 138 expert allergists and dermatologists in 2 rounds.

### Literature Search

The literature search focused on guidelines and reviews addressing management and monitoring of CU. The search was carried out on the web sites of the main allergology and dermatology scientific societies as well as in the main guideline repositories and in the PubMed database. In addition, a search was performed in PubMed with the following terms: ("Chronic Urticaria"[Mesh]) OR (Chronic Urticaria) AND (Control OR Remission OR Recovery of Function OR Disease Activity OR Urticaria Activity Score OR Urticaria Control Test). Guidelines and reviews from the last 5 years and clinical studies from

the last 10 years in Spanish or English were assessed. We selected the articles that proposed definitions of control and remission of CU or other terms, such as relapse, recurrence, flare-up, or exacerbation. In addition, we selected guidelines addressing disease monitoring, with emphasis on those that provided guidance on the use of PROs. The literature search was performed in July 2020. The details of the search are shown in Table S2. The evidence was qualitatively reviewed, summarized, and presented to the scientific committee to identify the debatable items.

## Results

The questionnaire contained 137 items divided into 3 blocks addressing controversial definitions and terms in CU (Table S3), available and recommended PROs in CU (Table S4), and recommendations on how to measure therapeutic objectives in CU (Table S5). The questionnaire was submitted to a panel of 147 experts, and 138 panelists responded to both rounds of evaluation. After 2 rounds of evaluation, a consensus was reached on 105 out of the 137 proposed items (76.6%) (agreement in 100 and disagreement in 5). Consensus was not reached on 32 items (Table S3-S5). No consensus was reached for 7 out of 8 items related to the best term to define reappearance of symptoms in an asymptomatic CU patient with or without treatment (Table S3). Key terms used in CU that need clarification and only 1 definition are summarized in Table 1.

The Figure shows an algorithm for assessment of CU that summarizes the consensus on recommended PROs and tools to assess disease activity and control and quality of life (QOL) in clinical practice and when to use them. This algorithm includes consensus items from block II (Table S4). Table 2

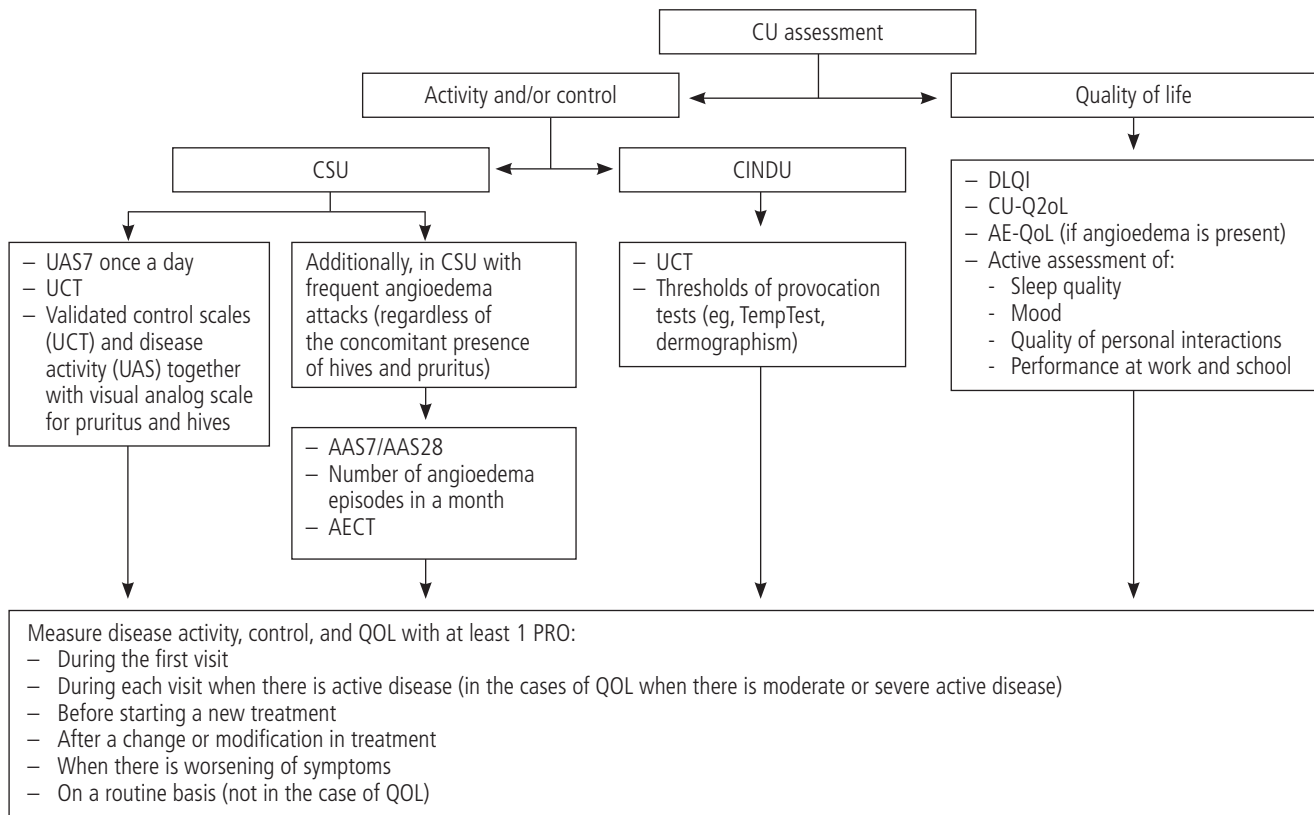
**Table 1.** Key Terms in Chronic Urticaria Requiring Clarification and a Single Definition

The best term to define the total absence of signs or symptoms of the disease when on treatment	• Control <sup>a</sup>
The best term to define the total absence of signs or symptoms of the disease in the absence of treatment	• Remission <sup>a</sup>
The term proposed to define the reappearance of symptoms in an asymptomatic CU patient while on treatment (no consensus).	• Flare-up • Break-out • Exacerbation
The best term to define the reappearance of symptoms in an asymptomatic CU patient in the absence of treatment:	• Relapse <sup>a,b</sup> • Recurrence • Recidivate

Abbreviation: CU, chronic urticaria.

<sup>a</sup>Terms for which consensus was reached.

<sup>b</sup>The panel reached a consensus on the term "relapse" as "recidiva" in Spanish.



**Figure.** Algorithm for chronic assessment of urticaria. AAS indicates Angioedema Activity Score; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; CINDU, Chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CU-Q2oL, Chronic Urticaria and Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; PRO, patient-reported outcome; QOL, Quality of life; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

summarizes definitions of control of CU (complete, good, partial, or absence), PROs that define this degree of control, time to confirm the degree of control in a patient treated with biological or immunomodulatory therapy, and management recommendations. The table includes mostly consensus items from block III (Table S5) and some consensus items from block I related to the definition of disease control (Table S3).

## Discussion

In this article, we review the concepts of disease control and remission, as well as other key terms used in CU, and evaluated guidelines and reviews addressing monitoring and treatment goals in clinical practice. A panel of allergists/allergologists and dermatologists with extensive experience in the management of CU reached a consensus on the definition of control and remission. In addition, the experts reached a consensus on aspects related to the assessment and management of CU and provided insights on how to monitor and manage the disease according to activity.

### Key Terms Used in CU That Require Clarification

Despite the fact that the definition of CU is well established [1,16], it is surprising that there is no agreed definition in the literature of key terms such as control and

remission, which are sometimes considered interchangeable in the literature [9]. This lack of consensus on terminology occurs in other fields of medicine, such as rheumatic diseases [20].

In clinical trials, symptom control and remission have been defined as an Urticaria Activity Score 7 (UAS7) of 0 while on treatment [9], although other definitions can be found, for example, “not being diagnosed with urticaria for at least 1 year during follow-up” [10] or “if a patient with CU never utilized medical services to treat urticaria for  $\geq 365$  days, even after using all the prescribed urticaria medicines” [11]. Similarly, the definition of control is not homogeneous in the literature [21–24]. Our panel agreed that the definition of these 2 concepts is not clear in the literature and reached a consensus on their definitions. The panel considered that the concepts of control and remission are different: control refers to patients without signs or symptoms of CU when on treatment, and remission refers to patients without signs or symptoms of CU when not on treatment. Accordingly, the panel agreed that complete control of CU could be defined as the absence of signs or symptoms of disease while the patient is receiving treatment for it, and remission can be defined as the total absence of signs or symptoms when the patient is not receiving treatment. In addition, there was agreement on a definition of good control, partial control, and absence of control, based mainly on the intensity of symptoms or signs while on treatment, always taking into account the assessment

of the clinical condition by both the treating physician and the patient (Table 2).

Recurrence and relapse are interpreted differently in the literature. In clinical trials with omalizumab in chronic spontaneous urticaria (CSU), relapse has been defined as UAS7  $\geq 16$  after symptom control and withdrawal of initial therapy [14]. However, relapse has also been considered to be the reappearance of CSU symptoms in complete responders and an increase in the UAS7 score compared with the value at the end of treatment with omalizumab in partial responders [15].

In other studies, CU recurring at least 6 months after cessation of effective therapy and disappearance of prior CU symptoms is referred to as recurrent CU instead of relapse [13]. In addition, in the Medical Subject Headings (MeSH) thesaurus (the National Library of Medicine's controlled vocabulary thesaurus used for indexing articles for the MEDLINE/PubMed database), the term recurrence is defined as the return of a sign, symptom, or disease after remission and includes the terms recrudescence and relapse [25]. The panelists were requested to agree on the differences between relapse, recurrence, and

Table 2. Definitions of Control of Chronic Urticaria and Recommendations on Management

	Complete control	Good control	Partial control	Absence of control
Definition	Absence of signs or symptoms of the disease while the patient is receiving treatment for it.	Decrease in symptoms or signs with treatment at an appropriate level as judged by both the physician and the patient.	Decrease in the intensity of the symptoms or signs of the disease with treatment, but without reaching an adequate level according to the opinion of the physician and the patient and without achieving a normal quality of life.	Absence of evident positive changes in the symptoms and quality of life of the patient after starting treatment (taking into account the evaluation of the clinical condition made by the treating physician and the assessment made by the patient).
PROs that define the degree of control in clinical practice <sup>a</sup>	<ul style="list-style-type: none"> <li>- UAS7 = 0 (does not apply in CINDU or angioedema).</li> <li>- UCT = 16.</li> <li>- Absence of angioedema (ASS7 or ASS28 = 0) if there is a previous history of angioedema.</li> <li>- Optimal quality of life (eg, DLQI = 0-1).</li> </ul>	<ul style="list-style-type: none"> <li>- UAS7 1-6 (does not apply in CINDU or angioedema).</li> <li>- UCT <math>\geq 12</math>.</li> <li>- Presence of angioedema (ASS7 or ASS28 &gt;0) that does NOT interfere with normal activity or does NOT have a high/significant impact on quality of life (if there is a previous history of angioedema).</li> <li>- Good quality of life (eg, DLQI = 2-5).</li> </ul>	<ul style="list-style-type: none"> <li>- Despite observing some clinical improvement, the patient continues with active disease by maintaining:               <ul style="list-style-type: none"> <li>- UAS7 &gt;6 (does not apply in CINDU or angioedema).</li> <li>- UCT &lt;12.</li> <li>- Presence of angioedema (ASS7 or ASS28 &gt;0) that interferes with normal activity or has a significant impact on quality of life (if there is a previous history of angioedema).</li> <li>- A significant impact on quality of life (eg, DLQI &gt;5).</li> </ul> </li> </ul>	No specific percentage or threshold of any PROs that serves to definitively define the absence of a response.
Time to confirm the degree of control in a patient with standard-dose second-generation H1-antihistamines <sup>b</sup>	2 wk	2 wk	2 wk	2 wk
Time to confirm the degree of control in a patient with up to 4-fold standard-dose second-generation H1-antihistamine <sup>b</sup>	4 wk	4 wk	4 wk	4 wk
Time to confirm the degree of control in a patient receiving biological therapy <sup>b</sup>	3-6 mo	3-6 mo	3-6 mo	6 mo

(continuation)

Table 2. Definitions of Control of Chronic Urticaria and Recommendations on Management (*continued*)

	Complete control	Good control	Partial control	Absence of control
Recommendations	<ul style="list-style-type: none"> <li>– A modification of the dosage regimen or change in treatment is recommended if there is a treatment-related adverse event.</li> <li>– If a decrease in the dosage regimen of a well-tolerated treatment in a patient with a complete response is desired, it is recommended to lower the dosage regimen when the patient presents a complete response for <math>\geq 3</math>-6 mo.</li> <li>– If a well-tolerated treatment is to be withdrawn in a patient with a complete response, it is recommended to withdraw it when the patient presents a complete response for <math>\geq 6</math> mo</li> </ul>	<ul style="list-style-type: none"> <li>– A modification of the dosage regimen or change in treatment is recommended:               <ul style="list-style-type: none"> <li>- When the patient has achieved a good response to treatment (but not a complete response), and more effective therapeutic alternatives are available.</li> <li>- Or there is a treatment-related adverse event</li> </ul> </li> <li>– It is not recommended to withdraw the treatment or lower the treatment dosage in a patient who has a good response (but not a complete response) and the treatment is well tolerated.</li> </ul>	<ul style="list-style-type: none"> <li>A modification of the dosage regimen or change in treatment is recommended</li> </ul>	<ul style="list-style-type: none"> <li>A modification of the dosage regimen or change in treatment is recommended</li> </ul>

Abbreviations: AAS, Angioedema Activity Score; CINDU, chronic inducible urticaria; CU, chronic urticaria; DLQI, Dermatology Life Quality Index; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

<sup>a</sup>To assess the degree of control (complete control, good control, or partial control), it is recommended to use a validated questionnaire and complement it with an assessment by the treating physician, taking into account the patient's own assessment of his/her clinical condition as well.

<sup>b</sup>Scientific committee recommendation not specifically addressed in the questionnaire.

other, related terminology such as flare-up and exacerbation. The questionnaire was provided in Spanish; therefore, the conclusions cannot be directly transposed into English. The panel did not reach an agreement on the best term to define the reappearance of symptoms in an asymptomatic CU patient on treatment. The term with the highest degree of consensus (very close to agreement) is flare-up (“brote” in Spanish), with a greater degree of consensus than exacerbation (“*exacerbación*” in Spanish). In the MeSH thesaurus, symptom flare-up is defined as a transient exacerbation of symptoms of an existing disease or condition [26], which is in line with our panel consensus. On the other hand, the panel agreed that the best term to define the reappearance of symptoms in an asymptomatic CU patient in the absence of treatment is relapse (“*recidiva*” in Spanish), rather than recurrence (“*recurrencia*” in Spanish). In conclusion, we propose to use the terms relapse and flare-up (rather than exacerbation or recurrence) to describe the reappearance of symptoms in an asymptomatic CU patient in the absence of treatment or while on treatment, respectively. However, a consensus model specifically designed in English would be necessary to make this recommendation applicable to the English-language literature.

### CU Monitoring

Regarding the use of PROs, the panel agreed that there is a need to define which PROs are most indicated for use in daily clinical practice or whether there are specific situations where one can be used instead of another. Guidelines are

not consistent on which PROs should apply to CU patients or on when they should be applied in the course of the disease [1,4,5,16,27,28].

In line with the EAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines [1], the panel agreed that in daily clinical practice, it is advisable to use PROs to help measure CU activity, the degree of CU control, and the QOL of patients with CU. Besides, the EAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines suggest using the UAS7 and the Angioedema Activity Score (AAS) to assess disease activity, the Urticaria Control Test (UCT) to assess disease control, and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and Angioedema Quality of Life Questionnaire (AE-QoL) to assess impairment of QOL in patients with CSU [1]. The panel's agreements are generally in line with these recommendations, although they added recommendations for assessment of chronic inducible urticaria (CINDU) based on assessment of thresholds with specific diagnostic tests (Figure). Considering the agreed items on the use of PROs, the scientific committee designed an algorithm that summarizes the consensus on recommended PROs and tools to assess disease activity, disease control, and QOL and when to use them (Figure). This algorithm can be a simple and useful tool in clinical practice when caring for a patient with CU.

In general, the panel agreed that it is advisable to measure the activity and control of CU using PROs on a routine basis. Conversely, there was no consensus on the need to measure QOL routinely. This difference may be explained by the

fact that tools used to measure QOL are time-consuming and difficult to administer in clinical practice, where time is limited. In addition, the activity of CU is usually associated with impairment of QOL [18,29], and the panel might have considered that measuring QOL is somewhat redundant and that it may be better to prioritize monitoring of disease activity and control. On the other hand, the EAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines recommend that patients with CU should be assessed for disease activity, impact, and control at every visit [1]. Our panel recommended assessments at specific points during the course of the disease (Figure 1) and on a regular basis rather than at every visit. Again, the panel tends toward a more practical, down-to-earth point of view than the guidelines.

### Therapeutic Goals

Considering the objectives of therapy for CU, the panel reached a consensus on a key point that may guide the decision-making process when managing CU patients, namely, the therapeutic objective of CU should be to achieve complete control of the disease. The panel also considered that if complete control is not achieved after treatment alternatives have been exhausted, the therapeutic objective should be good control, that is, minimum disease activity. Partial control is not an optimal therapeutic goal. The panelists agreed on the thresholds recommended in the PROs to define complete and good or partial control of CU in clinical practice. This definition of control based on PROs may be more useful in clinical practice than the broad definition agreed previously in block I. The definitions of control from these 2 perspectives are presented in Table 2, which also shows the consensus on the timeframe needed to confirm the degree of control in a patient on treatment. The scientific committee considered that this timeframe applies only for biological therapy and agreed that the time required to confirm the degree of control in a patient with standard-dose and up to 4-fold standard-dose second-generation H1-antihistamines is shorter, ie, 2 and 4 weeks, respectively (Table 2). The panel defined absence of response as the absence of evident positive changes in the patient's symptoms and QOL after starting treatment, as assessed by both the treating physician and the patient. The recommended duration of absence of response to confirm a treated patient as a nonresponder is 6 months. Again, the scientific committee considered that this time applies only to the biological therapy available for CU. The panel also agreed that there is not yet a specific percentage or threshold of any PROs that serves to define the absence of a response; therefore, a specific percentage or threshold of some PROs must be determined to define absence of response. Finally, the panel considered 6 months to be the recommended duration of the absence of signs and symptoms of CU to confirm that a patient without treatment is in remission.

In relation to QOL (regardless of activity and/or level of disease control), the panel considered it necessary to administer a QOL questionnaire (eg, DLQI, CU-Q2oL) to actively investigate sleep quality, mood, quality of personal interactions (family, friends, sexual and emotional life), and performance at work or school. These PROs and tools were added to the Figure to make them easier to remember.

Finally, the panelists agreed to modify the dosage regimen or change treatment, mainly in 3 situations: when the patient does not respond to treatment; when he/she presents a partial or a good response to treatment (but not a complete response) and more effective therapeutic alternatives are available; or when he/she has achieved a good or a complete response to treatment but there is a treatment-related adverse event. The scientific committee summarized these consensus items as recommendations in Table 1.

Our study is subject to a series of limitations, most of them related to the Delphi design, which prevented us from including the individual opinions of the panelists or discussing the statements in detail. In addition, since the questionnaire was designed by a limited number of experts, some issues may be overlooked. The panel selection is another limitation of the Delphi methodology. However, the panelists were carefully selected, and we believe that their expertise is undoubted and that their opinion reflects the predominant opinion among other experts in this field. The possible influence of the scientific committee on the results is limited, since they did not take part in the voting process. Furthermore, given that the questionnaire was designed in Spanish, recommendations on terminology are not directly transposable into English. Nevertheless, this local initiative may guide future international consensus focusing on these inconsistencies in terminology.

## Conclusions and Recommendations

In conclusion, we propose a consensus definition of control and remission of CU and clarify other key terminology issues. Additionally, we provide insights on how to monitor and manage CU according to disease activity, emphasizing that the therapeutic objective should be complete disease control. Gathering together consensus items, the scientific committee developed an algorithm and a table that might prove useful in clinical practice for optimizing the decision-making process during the clinical management of patients with CU. Based on the consensus items, the scientific committee proposed the following main recommendations:

- Complete control of CU should be defined as the absence of signs or symptoms of disease while the patient is receiving treatment for it; remission can be defined as the total absence of disease signs or symptoms in the absence of treatment.
- The term relapse (rather than exacerbation) should be used to describe the reappearance of symptoms in an asymptomatic CU patient in the absence of treatment.
- The term flare-up (rather than recurrence) should be used to describe the reappearance of symptoms in an asymptomatic CU patient while on treatment.
- In daily clinical practice, it is advisable to use at least 1 PRO to help measure the activity of CU, the degree of control, and patients' QOL. An algorithm is proposed to help clinicians follow this recommendation.
- Complete control of CU in clinical practice may be defined as:
  - UAS7 = 0 (does not apply in CINDU or angioedema).
  - UCT = 16.
  - Absence of angioedema (ASS7 or ASS28 = 0) if there is a previous history of angioedema.

- Optimal QOL (eg, DLQI = 0-1).
- Good control of CU in clinical practice may be defined as:
  - UAS7 1-6 (does not apply in CINDU or angioedema).
  - UCT  $\geq$ 12.
  - Presence of angioedema (ASS7 or ASS28 >0) that does NOT interfere with normal activity or does NOT have a high/significant impact on QOL (if there was a previous history of angioedema).
  - Good QOL (eg, DLQI = 2-5).
- Partial control of CU in clinical practice may be defined as follows:
  - Despite observing some clinical improvement, the patient continues with active disease by maintaining:
    - UAS7 >6 (does not apply in CINDU or angioedema).
    - UCT <12.
    - Presence of angioedema (ASS7 or ASS28 >0) that interferes with normal activity or has a significant impact on QOL (if there is a previous history of angioedema).
    - A significant impact on QOL (eg, DLQI >5).
- The time necessary to confirm the degree of complete, good, or partial control in a patient receiving biological therapy is 3-6 months.
- The therapeutic objective of CU should be to achieve complete control of the disease. If complete control is not achieved after treatment alternatives have been exhausted, the therapeutic objective should be good control, with every attempt made to accomplish minimum disease activity. Partial control is not an optimal therapeutic goal.

Further studies to determine whether these tools and recommendations are useful in clinical practice and how they may improve clinical practice are warranted.

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