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RESEARCH ARTICLE

Definition of Uveitis Refractory to Treatment: A Systematic Review in the Absence of a Consensus

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ABSTRACT

Purpose: To evaluate the different definition of refractoriness in uveitis in the literature.

Methods: We systematically searched the literature in order to identify definitions of refractory non-infectious uveitis in adult patients. A search strategy in the databases of MEDLINE and Scopus was used to find articles published between January 2005 and October 2018.

Results: Definitions of corticosteroids-refractoriness were related to two main concepts: persistence of inflammation despite the use of corticosteroid and recurrences above a dosage threshold. In terms of immunomodulatory therapy and biologic agents, we observed a great variety of definitions: persistence of inflammation, number of attacks, side effects or complications, symptoms, and best-corrected visual acuity.

Conclusions: The results of this systematic review demonstrate the current lack of consensus on the definition for refractory uveitis, regardless of the treatment being used and revealed a new terminology based on a comprehensive and operational definition for each specific category of refractoriness.

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Uveitis is a group of inflammatory diseases with potential severe vision-threatening complications, including legal blindness.[1] Current therapeutic options include corticosteroids (CS), immunomodulatory therapy (IMT) and, more recently, biologic agents (BIO), frequently applied using a "step-ladder approach."[2]

The decision regarding when to escalate therapy is based on the response or efficacy of each treatment step. Importantly, the time elapsed until the control of inflammation is a cornerstone of the functional and anatomical prognosis.[2] Therefore, it is crucial to reach a consensus for defining refractoriness to treatment in uveitis patients, in order to timely adjust therapy, leading to better outcomes.

The lack of a standard definition for refractory uveitis or treatment failure also affects research evaluating new drugs for the subset of refractory patients. These studies present a challenge in terms of the protocol design, particularly for the selection of inclusion criteria and outcomes that can be appropriated in a specific field where a consensus has not been achieved.

A proposal for standardization of uveitis nomenclature[3] and guidelines for the use of CS, IMT, and/or BIO in uveitis was published a few years ago, including treatment indications, side effects, and contraindications.[2,4,5] However, there is no consensus about the definition of refractory uveitis.

Considering the growing number of publications in the area and the variability of the used terminology, even in the same study, we performed a systematic review of the current literature in order to identify definitions of refractory uveitis. In this article, we proposed a new terminology based on a comprehensive and operational definition for each specific category of refractoriness, with the aim of providing a framework for making decisions in clinical practice and for designing further research on new drugs for uveitis patients.

Methods

Search Strategy

This systematic review was conducted to identify the degree of clinical consensus in the definition of refractoriness, or lack of response, to the therapy on uveitis. The results are shown according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines for reporting systematic reviews.

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Supplemental data for this article can be accessed on the Publisher's website.

An electronic search was performed considering articles published between January 2005 and October 2018 in the digital databases of MEDLINE and Scopus. The decision of starting the analysis from 2005 was to include the SUN consensus.[3] Both databases were screened using the following search terms: ["uveitis" AND ("resistant" OR "refractory" OR "intractable" OR "treatment failure")] and filtered by language (English and Spanish). Subsequently, a manual search was conducted in order to eliminate duplicate articles.

Selection of the Studies

Articles were included for analysis if they fulfilled the following criteria: 1) enrolled adult patients with a diagnosis of noninfectious uveitis; 2) were published in English or Spanish; 3) included at least five subjects; 4) contained an explicit definition of refractoriness; 5) full text was available. A revision of the title and abstract of the retrieved articles was performed as a first step of the evaluation of studies eligibility, defining their relevance according to the selection criteria presented above. Following this, relevant studies and articles with no abstract available were screened extensively and a detailed evaluation of these manuscripts was conducted. Review articles concerning treatment of uveitis patients were also included if they had an explicit definition of refractoriness.

Data Extraction

All screened articles were independently reviewed by four of the study authors. Disagreements between authors, with respect to study inclusion, were resolved by consensus. Each study included in the final analysis was reviewed for the authors independently and the following data were extracted: refractory uveitis definition, first author's last name, publication year, study design, sample size, uveitis etiology, subjects included and interventions. For reporting purposes regarding the terminology used by authors, we extracted the most frequent cited term in the main text of each study. For analysis, each definition of refractory uveitis was assigned to the following groups: CS-refractory, IMT-refractory or BIO-refractory.

Proposed Definitions

Proposals for definitions of refractoriness to treatment in specific diseases were constructed, based on previous expert panel reports[3,4] plus the results of this systematic review (definitions most commonly used in literature) or the achievement of a consensus among the authors in cases in which published literature lacks significant data to elaborate a consistent definition. To formulate disease-specific definitions of refractoriness based on the reviewed literature, articles including patients with a specific condition were critically analyzed, and main concepts contained in the definitions were identified (such as persistence, attacks, subjective symptoms, BCVA, and ancillary tests).

Results

Literature Search and Selection of Trials

The database search yielded a total of 1776 publications, and these were curated as detailed under Methods. After the selection process and application of our eligibility criteria, 91 studies were subjected to analysis (supplemental references) as seen in **Methods** and PRISMA flow diagram in Figure 1. It is worth mentioning that of the 895 excluded studies, according to the criteria established in Methods, 93 of these correspond to case series.

Study Characteristics

We identified the following number of studies referring to refractory uveitis (supplemental references): CS-refractory (10 studies), IMT-refractory (25 studies) and BIO-refractory (42 studies). There were 14 studies that included more than one definition: CS/IMT-refractory (5), CS/BIO-refractory (1), IMT/BIO-refractory (6) and CS/IMT/BIO-refractory uveitis (2) (Figure 1). For this analysis, all studies with more than one definition were included in each group shown in Table 1.

Study designs were mostly case series (54/91) and prospective (42/91) studies, with a broad range of sample size, including from 5 to 500 patients. In addition, 13 cohort studies, 7 randomized controlled clinical trials (RCT), 6 non-controlled clinical trials, 5 reviews, and 3 systematic reviews were included.

Terminology

Among the reviewed studies, there was no agreement in the terminology for describing the phenomenon of lack of response to each treatment strategy. Indeed, five different terms were used for the evaluation of CS or BIO or IMT.

In studies that included definitions of CS, IMT and BIO refractoriness, the most common terminology used was *refractory* (CS: 33.3%; IMT: 42.1%; BIO: 29.4%), *failure* (CS: 27.8%; IMT: 28.9%; BIO: 33.3%), *no response* (CS: 11.1%; IMT: 7.9%; BIO: 17.6%), *ineffective* (CS: 16.7%; IMT: 10.5%; BIO: 11.8%) and *resistant* (CS: 11.1%; IMT: 10.5%; BIO: 5.9%) (Table 1).

Definition of CS-refractoriness

CS-refractoriness was defined based on the outcomes during induction and tapering phases of steroid treatment. In all of these studies, authors considered refractoriness in patients who presented active inflammation within a certain period of time[6] or above a specific threshold of prednisone dose.[6–8] Specific definitions for relapse or clinical activity were not included in the analyzed studies.[9]

In regard to tapering phase, in 5 out of 18 studies the definition of refractoriness was related to the dependence of a high maintenance dose of prednisone. In these reports, cut-offs used for defining the treatment response were 10 mg/day and 20 mg/day [Supplemental references 3, 5, 6]. In the case of topical CS treatment, the need of more than 2 drops of prednisolone acetate was found to be a parameter of treatment failure (Supplemental references 80, 82).

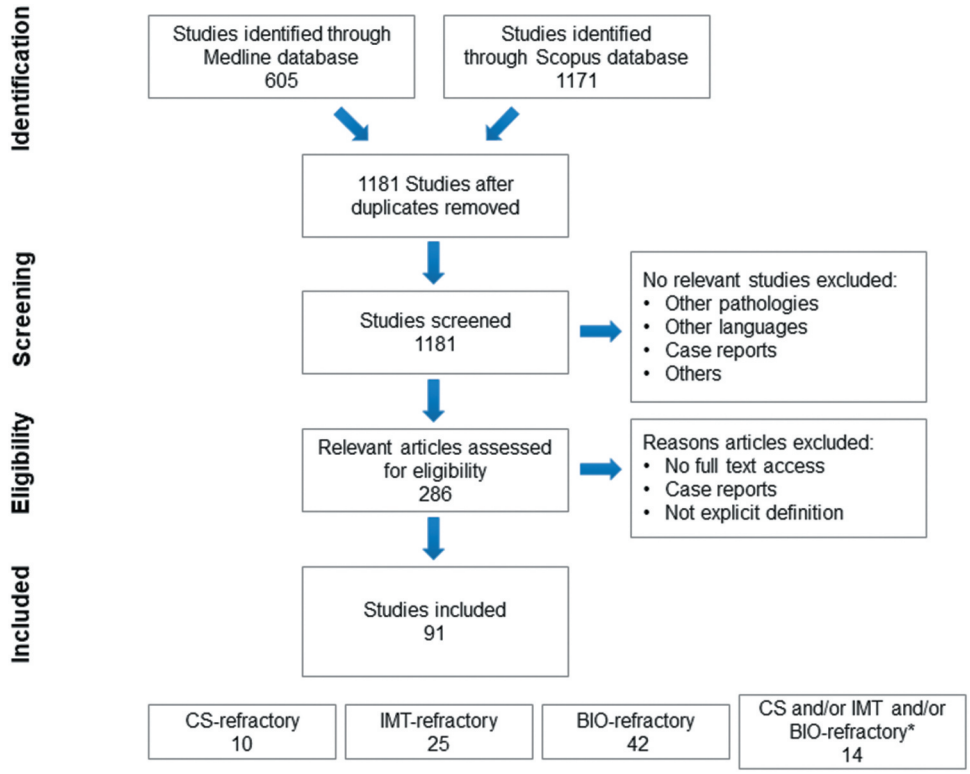

Figure 1. Prisma flow diagram of the methodology used to select the articles that define uveitis treatment refractoriness. According to the terms mentioned in methods, 1776 articles were identified from the MEDLINE and SCOPUS databases. Subsequently, the non-relevant studies were eliminated, 286 articles were evaluated to be finally selected, for which those that had no explicit definition among other reasons were excluded. Finally, we select 91 articles, which we divide according to the definition of refractoriness associated with the treatment: CS-Refractory, IMT-Refractory and BIO-Refractory. *14 articles included more than one definition (5 CS/IMT, 1 CS/BIO, 6 IMT/BIO and 2 CS/IMT/BIO). CS: corticosteroids; IMT: immunomodulatory; BIO: biologics.

In summary, definitions of CS-refractoriness were related to two main concepts: persistence of inflammatory activity despite the use of CS and uveitis flare-up during treatment with prednisone/prednisolone dose above a dosage threshold.

Definition of IMT and BIO-refractoriness

For data analysis regarding IMT and BIO refractoriness, due to the number of studies and the observation of multiple definitions, a summary of the main concepts included in each definition was performed. Persistence of the inflammation despite the use of the study medication (either IMT or BIO) and the number of attacks were the most included concepts in each definition (Table 1). Other outcomes considered for the definition of treatment response were as follows: side effects or complications (8 studies for IMT-refractoriness and 7 BIO-refractoriness), subjective symptoms (1 study for IMT-refractoriness and 1 study for BIO), best-corrected visual acuity (7 studies for BIO and 23 for IMT), addition of new therapy (5 studies for IMT-refractoriness and 3 BIO-refractoriness) and CS-tapering (15 studies for IMT and 17 for BIO).

Interestingly, the majority of the retrieved studies included clinical variables for defining refractoriness. Only 9 (23.7%) studies in IMT group, 20 (39.2%) studies in BIO and 7 studies (38.9%) in CS group introduced an ancillary in order to evaluate treatment outcomes, such as electrophysiology (ERG), Optical Coherence Tomography (OCT) or Fluorescein angiography (FA) (Table 1). In these 36 studies, the tests used were as follows: for CS-refractory, one publication mentions OCT [Supplemental references 1] and six mentioned OCT and FA [Supplemental references 4, 8, 9, 79, 81, 83]. In the case of IMT-refractoriness, two studies included FA [Supplemental references 12, 31], four OCT [Supplemental references 13, 20, 30, 33], and three other OCT and FA [Supplemental references 79, 81, 85]. Finally, for BIO-refractoriness, 4 articles used only OCT [Supplemental references 39, 51, 68, 73], 5 used only FA [Supplemental references 46, 53, 58, 71, 76], 10 used OCT and FA [Supplemental references 45, 48, 67, 69, 70, 72, 74, 75, 83, 85] and 1 used OCT and ERG [Supplemental references 44].

Discussion

In the work, by performing a systematic review, several definitions were found for treatment refractoriness in uveitis patients. As shown above, a broad variety of terminology has been considered for inclusion criteria in order to identify a poor clinical course of the disease after treatment initiation, such as refractory, resistant, failure, ineffective, etc. The use of different terms may induce some confusion among clinicians and investigators. Moreover, it may potentially generate heterogeneous data and thus, limit the comparability of clinical research among different centers or settings.[3]

The most common terms or expressiones used were refractory (CS and IMT) and failure (BIO). There were neither clinical nor semantic differences between both terms among

Table 1. Summary of the main concepts and methodology of the included studies of refractoriness to corticosteroids, immunomodulatory therapy, and biologics in noninfectious uveitis[£].

Study Design, n (%)	CS[1] (18 studies[§¥*])	IMT[2] (38 studies[§€*])	BIO[3] (51 studies[¥*€])
Cases series	12 (66.7)	22 (57.9)	26 (51.0)
RCT[4]	0 (0.0)	4 (10.5)	4 (7.8)
Retrospective	9 (50.0)	19 (50.0)	28 (54.9)
Prospective	9 (50.0)	19 (50.0)	23 (45.1)
Sample size, mean (range)	46.5 (5–158)	39.0 (7–236)	69.9 (5–500)
Terminology, n (%)			
Refractory	6 (33.3)	16 (42.1)	15 (29.4)
Resistant	2 (11.1)	4 (10.5)	3 (5.9)
Failure	5 (27.8)	11 (28.9)	17 (33.3)
No response	2 (11.1)	3 (7.9)	9 (17.6)
Ineffective	3 (16.7)	4 (10.5)	6 (11.8)
Concepts, n (%)			
Persistence	11 (61.1)	27 (71.1)	30 (58.8)
Attacks	5 (27.8)	14 (36.8)	27 (52.9)
Side effects or complications	4 (22.2)	8 (21.1)	7 (13.7)
Subjective symptoms	0 (0.0)	1 (2.6)	1 (2.0)
BCVA[5]	4 (22.2)	7 (18.4)	23 (45.1)
Threshold	5 (27.8)	1 (2.6)	0 (0.0)
Addition of new therapy	4 (22.2)	5 (13.2)	3 (5.9)
CS tapering	N/A[6]	15 (39.5)	17(33.3)
Evaluation method, n (%)			
Clinical only	11 (61.1)	29 (76.3)	31 (60.8)
Clinical plus ancillary test	7 (38.9)	9 (23.7)	20 (39.2)

[1]CS = corticosteroids
[2]IMT = Immunomodulatory
[3]BIO = Biologics
[4]RCT = Randomized controlled Clinical trial
[5]BCVA = Best-corrected visual acuity
[6] N/A = Non-applicable
[£]Supplemental References
[§]5 articles included definition for CS and IMT
[¥]1 article included definition for CS and BIO
[*]2 articles included definition for CS, IMT and BIO
[€]6 articles included definition for IMT and BIO

the reviewed reports. Hence, we propose *refractory* as appropriate concepts to describe the lack of or insufficient response to therapy in patients with uveitis.

It is important to point out that uveitis represents a list of different conditions, with particular clinical features, follow up requirements, treatment strategies and natural history.[9] While several diseases are feasible of full evaluation from a clinical perspective, some conditions might be followed up by carrying out ancillary test, due to the evidence of subclinical levels of inflammation that may determine worse clinical outcomes (i.e. Birdshot, VKH).[10,11] In this regard, 36 studies mentioned ancillary test in the definition of refractoriness, including FA, OCT, and ERG.

Refractoriness to CS Treatment

Two overall definitions of refractoriness to CS-treatment were found. Patients who remain active despite the use of CS and patients treated with an equivalent prednisone dose greater than 10 mg/day and having a reactivation or need of a dose greater than 20 mg/day to stop the progression of the disease.[6,7,11] Each clinical situation represents a specific subset of patients, with a different timing in the disease progression (treatment induction *versus* medication tapering) and a probable distinctive pathogenic mechanism ("total" refractoriness versus "partial" refractoriness or dependence in the later definition).[12–14] In the case of topical CS treatment, Niemeyer KM *et al* [Supplemental references 80] and Kim JS *et al.* [Supplemental references 82] clarify that for anterior chamber inflammation, a need of more than 2 drops of prednisolone acetate was found to be a parameter of treatment failure.

Refractoriness to BIO/IMT

In brief, two main concepts of refractory uveitis were included in reports: persistence of the inflammation (30 for BIO and 27 to IMT) and the number of attacks during the treatment (27 and 14, respectively).

To define refractoriness to these therapeutic strategies, either IMT or BIO, authors have included some concepts based on the specific disease considered in the studies. For instance, the number of attacks incorporated as an endpoint for refractoriness in some reports that implies a recurrent nature of the conditions included for the analysis, such as Behçet disease or HLA-B27 related uveitis. In that setting, it represents an appropriate endpoint, but it may not be representative or useful in subjects with diseases where the natural history does not have clinical relapses, such as Birdshot chorioretinopathy, or in patients who present typical acute conditions, such as Posner-Schlossman or multiple evanescent white dot syndromes.

In addition, it was found visual acuity as an endpoint for establishing refractoriness in 30 studies (23 for biologicals and 7 for IMT) (Table 1). In this regard, this functional outcome is a result of multifactorial variables, not just a direct consequence of controlling the inflammation. For instance, anatomical complications, such as macular edema or cataract, or the presence of co-morbidities can potentially impact on the visual findings, despite the control of the inflammatory process.[15–17]

Proposed Definitions for Refractoriness of Treatment in Uveitis Subtypes

Uveitis comprises a group of very heterogeneous diseases, for this reason, we hypothesize that the outcomes and lack of response to treatment should be individualized for each disease. In this regard, we propose some definitions related to refractoriness to treatment according to disease type (Table 2). For Behçet disease, we incorporate the concepts of relapses and ancillary test (FA to evaluate vasculitis), since these notions were the most commonly used in the reviewed literature (17 and 11 out of 31 articles included recurrences and tests in their definitions, respectively). In Birdshot chorioretinopathy, a definition of refractoriness was developed considering the use of ancillary testing to evaluate the well-known slow progression (i.e., visual fields and electroretinography). In sarcoidosis cases, clinicians should pay special attention to the development of chronic inflammation in order to define treatment refractoriness. The proposed definition of refractoriness for VKH includes the most important ocular feature in this condition, which is the presence of areas of retinal detachment or subretinal fluid.

Furthermore, special attention should be taken in the process of quantification of disease activity, which is performed by

Table 2. Proposed definitions for refractoriness of treatment in a patient with uveitis for different diseases.

Disease	Definition of uveitis refractory to treatment	Rationale for suggesting definition
Behçet Disease	Presence of intraocular inflammation relapses despite treatment. A relapse is defined according clinical signs (anterior chamber and or vitreous) and/or ancillary testing (fluorescein angiogram for vasculitis, and OCT for macular edema).	Based on the literature reviewed in this study*
Birdshot chorioretinopathy	Evidence of persistent clinical inflammation (vitritis, papillitis, vasculitis) and/or disease subclinical progression on ancillary test (visual fields, electroretinography).	Based on previous panel reports** and a consensus among the authors.
Sarcoidosis	Presence of chronic intraocular inflammation on clinical examination (persistent inflammation or relapse in less than 3 months after treatment discontinuation) and/or ancillary testing (fluorescein angiogram for vasculitis, and OCT for macular edema).	Based on previous panel reports** and a consensus among the authors.
Vogt-Koyanagi-Harada	Absence of inflammatory improvement (namely not achieving a two-step decrease in the level of inflammation or a decrease to grade 0) and/or persistence of retinal detachment, despite 4 to 6 weeks of prednisone therapy, or to develop chronic recurrent stage of the disease.	Based on previous panel reports** and a consensus among the authors.

*Supplemental References: 7, 9, 12, 14, 18, 19, 21–23, 27, 32, 35, 38, 41, 42, 44, 49, 57, 60, 64, 65, 67, 69, 71, 75, 76, 81, 83, 85, 87, 90.
**References: 3, 4.

the clinician. In that sense, Diaz-Valle group described an index called UVEDAI to objectively categorize the degree of activity and severity, using a standardized approach based on important clinical features, such as best-corrected visual acuity, inflammation of the anterior chamber, intraocular pressure, and central macular edema.[18]

Study Limitations

Data retrieved from this systematic review mostly come from retrospective case series studies, mainly with small sample size. Therefore, bias related to this design may be present, since definitions and terminology could be created and used after the clinical situation occurs and thus reported with limited accuracy. In that sense, the consensus of refractoriness should be addressed and pre-defined in order to be included since the beginning in the conduction of both retrospective and prospective clinical studies. The major problem in such review is that it concerns practices from the past relying mainly on clinical grounds and that it does not include precise ancillary tests capable to show subclinical inflammatory involvement, which are very slow to be granted entry in a precise appraisal of inflammation, a very much desirable step toward which uveitis clinical research should be aimed.[19] Taking an analogy it concerns only the peak of the iceberg (clinical signs and limited ancillary tests), when the investigative modalities of the hidden part of the iceberg are still neglected at large although they would greatly contribute to better define the terms we analyzed here.

Conclusions

First, we propose the use of the terms refractory or failure, in an interchangeable fashion. Also, based on the variety of clinical features in each category of uveitis and the broad range of concepts for constructing definitions found in this systematic review, we propose a general definition of refractoriness based on the consensus published elsewhere[3,4] and, additionally, a disease-specific definition of treatment failure that provides relevant aspects in the follow-up and clinical outcomes in each cause of uveitis. Therefore, patients who do not achieve a 2-step decrease in the level of inflammation in anterior chamber and/or vitreous despite the use of a specific treatment scheme must be considered refractory.

Nevertheless, studies for defining disease-specific criteria for refractoriness must be conducted in order to have reliable endpoints for each particular subset of patients with uveitis. In this regard, clinical variables or ancillary tests described as relevant in terms of final outcomes such as retinal detachment or ERG for monitoring patients with VKH and Birdshot chorioretinopathy, respectively,[10,20] must be considered for specific-disease definitions of refractoriness.

Finally, for CS-refractoriness, we proposed a two-category definition, based on the timing and dosage of CS at the moment of the response categorization. Then, patients who remain active despite the use of CS during induction phase may be considered with an *initial* CS-refractoriness and a category of late CS-refractoriness may be used for subjects who achieve control of the inflammation and have a further reactivation after tapering of CS (maintenance phase), with an equivalent prednisone dose greater than 10 mg, which represents a dose that it has been described as safer in a chronic therapy basis.[12–14]

Implications for Practice

Treatment response is a relevant outcome for the evaluation of uveitis patients in both clinical setting and research. However, the lack of standardized criteria for the definition of treatment refractoriness leads to further difficulties at the time to interpret results and translate them to clinical practice. Using a systematic strategy, a search for definitions of "treatment refractoriness" in uveitis patients was conducted, in articles from January 2005 to October 2018. The present study provides a valuable summary and an approach for an universal definition for treatment refractoriness for uveitis in order to obtain reproducible data in future studies and to categorize the treatment effectiveness in the clinical practice. In addition, authors propose a set of practical definitions for specific conditions, which are expected to be used in a day-to-day clinical practice and in the context of research studies.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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