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ORIGINAL PAPER

Assessment of measurement methods of posterior inflammation in stromal choroiditis: the value of quantitative outcome measures versus the presently qualitatively based paradigm

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Abstract

Purpose To assess posterior inflammation using a fluorescein (FA)/indocyanine-green angiography (ICGA) scoring system, and compare them to the presently recommended outcome measure, the standardization of uveitis nomenclature vitreous haze score (SUN-VH) in stromal choroiditis.

Methods This was a retrospective study on patients with a diagnosis of ocular sarcoidosis(OS), ocular tuberculosis(OT), Birdshot retinochoroiditis(BRC) and Vogt–Koyanagi–Harada disease(VKH) seen in the Centre for Ophthalmic Specialized Care, Lausanne, Switzerland. Angiography signs were quantified according to an established FA/ICGA scoring system. Vitritis was assessed using SUN-VH. Results were compared.

Results 65 newly diagnosed patients (128 eyes) with stromal choroiditis were included. Angiographic scoring showed variable degrees of choroidal versus retinal involvement (87% for OS, 72% for OT, 62.5% for BRC and 100% for VKH). On the other hand, a mere 22 of 128 eyes (17%) showed a SUN-VH score ≥ 2 necessary for inclusion in clinical trials. Moreover, FA/ICGA values followed a normal distribution curve and presented inter-examiner variations greater than 1-SD in only 8.4% of cases. SUN-VH values' distribution was non-normal and showed inter-examiner discrepancies greater than 1-SD in 51.7% of cases.

Conclusion This study highlights the precise measurement of global posterior inflammation achieved by a dual FA/ICGA scoring system in stromal choroiditis. In contrast, SUN-VH scale appears imprecise and inadequate, as only a minute percentage of the studied eyes could have been included in a clinical trial based on this criterion. To evaluate posterior intraocular inflammation meaningfully in stromal choroiditis, the use of dual FA/ICGA is strongly advised and should replace the presently recommended SUN-VH system.

Keywords Uveitis · Choroiditis · Fluorescein angiography · Indocyanine-green angiography · Vitritis · Intraocular inflammation · Guidelines

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Introduction

The measurement of inflammation has grown to become a crucial part of evaluating uveitic diseases

[1]. Indeed, there are numerous advantages in using scores in ocular inflammation: to support diagnosis, improve follow-up, reduce personal bias, facilitate communication between specialists, and analyze the data in clinical trials [2]. But to serve so many purposes, a scoring method must adhere to a number of requirements. It must be sensitive enough to investigate the disease studied, objective enough to be reproducible, and fine-enough to allow detection of subtle changes such as treatment response or disease progression [3].

We will use the aforementioned criteria to assess and compare two measurement methods of inflammation: the standardization of uveitis nomenclature vitreous haze score (SUN-VH) and the dual fluorescein/indocyanine green (FA/ICGA) angiography score. The SUN-VH, as described by Robert B. Nussenblatt et al., is currently the recommended and only FDA approved measurement method of posterior segment inflammation for clinical trials, and relies on an assessment of the fuzziness of the fundus under binocular indirect ophthalmoscopy. Twenty years ago, in his Posterior Segment Intraocular Inflammation Guidelines [4], John Forrester considered it the most reliable sign of posterior segment inflammation, but already acknowledged that in some cases; however, vitreous haze was minimal and recognized that fundus changes may allow a better assessment and follow-up. The FA/ICGA scoring system is a more recent method of grading inflammation both in the retinal and the choroidal compartments that was first described by the Angiography Scoring for Uveitis Working Group in 2010 [5]. It is based on the analysis of both fluorescein and indocyanine green angiographic signs using a specific grading scale.

The value of a test, however, not only depends on the test itself, but also on the specific set of diseases it is destined for. For this reason, we have chosen to study a group of diseases in which inflammatory signs tend to be confined to the depth of the posterior segment. Stromal choroiditis is a subtype of uveitis entities in which the inflammatory process seems to preponderantly involve the choroidal stromal structures. This group encompasses ocular sarcoidosis (OS) and ocular tuberculosis (OT), both conditions for which the choroidal stroma is one possible location of these two systemic diseases. It includes also Birdshot retinochoroiditis (BRC), and Vogt–Koyanagi–Harada disease (VKH), both conditions where disease starts electively from choroidal stromal structures and, therefore, are called primary stromal choroitides [6]. Yet, due to its often subtle and even occult lesions as well as presence of limited vitritis, stromal choroiditis is difficult to assess and remains underdetected and underdiagnosed [7, 8]. Hence, we will examine the value of the FA/ICGA score in this entire group of diseases, assess it against the current standard (SUN-VH), and explore its potential use for clinical trials.

Methods

Inclusion criteria

We retrospectively surveyed all uveitis cases managed at the Centre for Ophthalmic Specialized Care in Lausanne, Switzerland, between 1995 and 2017. Amongst those 1934 patients, we only retained newly diagnosed patients with stromal choroiditis including OS, OT, BRC and VKH for whom information was available for first presentation of initial onset disease, having sufficient data to calculate both studied scores. Follow-up cases with prior diagnosis were not included in this study.

Diagnosis

All included patients underwent a typical complete uveitis work-up at presentation and were diagnosed according to the published and recognized criteria for their respective diseases.

For ocular sarcoidosis (OS), previously published diagnostic criteria were used [13]: mutton-fat keratic precipitates (KPs)/small granulomatous KPs and/or iris nodules (Koeppe/Busacca), trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS), vitreous opacities displaying snowballs/strings of pearls, multiple chorioretinal peripheral lesions (active and/or atrophic), nodular and/or segmental peri-phlebitis (± candlewax drippings) and/or retinal macro-aneurism in an inflamed eye, optic disc nodules/granulomas and/or a solitary choroidal nodule, and bilaterality. Laboratory investigations were also used to elicit or confirm the diagnosis of OS, including a tuberculin skin test for BCG-vaccinated patients to show anergy, serum angiotensin converting enzyme (ACE) levels, serum lysozyme, liver enzymes, and a chest X-ray.

For ocular tuberculosis (OT), the diagnostic criteria included the presence of a compatible uveitis with posterior involvement with a PPD skin test of more than 15 mm of induration and/or a positive interferon-gamma release assay (IGRA) and exclusion of any other known cause of uveitis [11, 12].

For Birdshot retinochoroiditis (BRC), the following recently published diagnostic criteria were followed (9) including retinal vasculitis in small and large veins in one or both eyes, vitritis in one or both eyes, visual field abnormalities in one or both eyes, ICGA lesions in both eyes (required), presence of HLA-A29 antigen (required), with or without oval, depigmented birdshot lesions [9].

For Vogt–Koyanagi–Harada disease (VKH), diagnostic criteria included the presence of bilateral (mostly granulomatous) uveitis with exudative retinal detachments, ICGA signs of choroiditis characterized by the presence of evenly disposed hypofluorescent dark dots (HDDs) and vasculitis of the choroidal vessels, absence of ocular trauma and exclusion of any other known cause of uveitis [10].

Scoring methods

Both the SUN-VH score and the dual FA/ICGA score were calculated on the day of presentation using the following protocols.

FA/ICGA procedure and scoring

Fluorescein and indocyanine green angiography were performed using a standard protocol described previously [16]. In brief, patients were first investigated to exclude auto-fluorescence, and pre-injection fluorescence was identified with high flash intensity, and red-free images of the posterior pole were taken. An initial bolus of 4 mg of indocyanine green (ICG) (Cardiongreen, Peaselt, Loeri, Germany) diluted in 5 ml of saline for injection was given intravenously. For the first three minutes post-injection, early phase images were recorded using a Heidelberg Retina Angiograph, HRA 2 (Heidelberg Engineering Inc., Heidelberg, Germany). At 10 ± 3 min post-injection, posterior pole and eight panoramic ICGA frames of the periphery were taken. The latter constitute the intermediate phase images. A 5 ml solution containing 500 mg of fluorescein sodium was then injected to the patients and early FA frames were recorded up to 2 min. At 7–10 min post-fluorescein injection, posterior pole and eight panoramic frames of the periphery were taken. At 20 ± 3 min post-injection, posterior pole and eight panoramic ICGA frames of the periphery were again taken (late ICGA frames).

For scoring, FA and ICGA images were reviewed and scored by two independent clinicians using a validated FA/ICGA grading scale [5, 17]. In the latter, characteristic FA findings such as macular edema, optic disc hyperfluorescence, retinal vascular staining and leakage, capillary leakage, retinal capillary non-perfusion, neovascularization of the optic disc or elsewhere, pinpoint leaks, retinal staining and subretinal pooling were noted on a scoring sheet, and the points attributed to each FA finding were added up to obtain a total score with a maximal possible score of 40. Similarly, ICGA findings including choroidal vasculitis, early stromal vessel hyperfluorescence, hypofluorescent dark dots (HDD) or areas, and hyperfluorescence of the optic disc were noted with a maximal possible score of 20. The ICGA being made of half as many scoring items as FA, it was given a coefficient of 2 to obtain a comparable weight to that of FA. Any difference between the two independent markers was determined and averaged. Both scores were compared to determine the predominance and contribution of both the retinal and choroidal compartment and any differences between the independent two readers were determined and then averaged.

SUN-VH scoring

Fundal views of all involved eyes were evaluated using the SUN-VH grading scheme ranging from 0 to 4 (Fig. 1) [14], by two independent masked clinicians. The two independent results were compared and subsequently averaged to obtain the SUN-VH score out of a maximum of 4, reflecting vitreous activity [15].

Score	Description	Clinical Findings
0	Nil	None
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details hazy
3	Moderate	Posterior pole very hazy
4	Severe	Posterior pole barely visible

Fig. 1 Grading Scheme for Vitreous Haze as per SUN

Statistics

It was assumed that if both tests can be used to assess the equivalent components in the inflammatory process, then all results should follow a line defined by the simple equation x = y, in which x and y are, respectively, the FA/ICGA score and the SUN-VH score for a same patient. Both calculation methods were tested against this paradigm to assess whether they are measuring the same component of the disease (Figs. 2, 3, 4, 5 and 6).

All score results were plotted on a histogram, and a normality test was used to determine if the scores followed a normal distribution.

The average for each score was calculated for all included patients, as well as for each subtype of disease (OS, OT, BRC and VKH) using the usual formula: $\bar{x} = \frac{n_1x_1+n_2x_2+\cdots+n_px_p}{n} = \frac{1}{n}\sum_{i=1}^{i=p} n_ix_i$.

Variance and standard deviations were calculated for both scores to test the degree of dispersion of the results and their statistical significance, using the normal variance formula: $V = \frac{1}{n}\sum_{i=1}^{i=p} n_i(x_i - \bar{x})^2$

Data dispersion was represented for both scoring systems as a boxplot, depicting the results through their quartiles, and a simple statistical test was performed to check whether 95% of results fall within 2 standard deviations of the average, thus validating the results.

For SUN-VH score, the percentage of patients showing a score of 2 or more was calculated to determine the proportion of patients who could show statistically relevant 2 grade improvement during a clinical trial.

Finally, the inter-examiner variability of both tests was expressed in terms of percentage of scores showing a discrepancy greater than one standard deviation between two independent examiners assessing the same eye.

Fig. 3 Average SUN-VH score and standard deviation by subtype of disease

	SUN-VH
OS	0.59 ±0.64
OT	0.77 ±0.72
BRC	1.56 ±0.79
VKH	0,79 ±0.72
Total	0.81 ±0.76

Results

Included eyes

Amongst the 1934 patients suffering from uveitis who were seen between 1995 and 2017 at the Centre for Ophthalmic Specialised Care, in Lausanne, Switzerland, 65 patients (128 eyes) were newly diagnosed cases of stromal choroiditis and had enough data to be included in the study. This group comprised 23 OS patients (46 eyes), 28 OT patients (54 eyes), 8 BRC patients (16 eyes) and 6 VKH patients (12 eyes).

Dual FA/ICGA score

Angiographic scoring showed that in OS, choroiditis (ICGA score) was predominant over retinitis (FA score) in 40/46 eyes (87%) versus 6/46 (13%) eyes with predominant retinitis over choroiditis. Mean angiographic scores were 14.2 ± 5 for ICGA (choroid) v. 7.3 ± 4.6 for FA (retina). For tuberculous chorioretinitis (OT), the choroid was predominantly involved in 39/54 eyes (72%) and the retina in 14/54 eyes (28%). Mean scores were 13.55 ± 7.14 for the choroid (ICGA) v. 6.97 ± 5.08 for the retina (FA). For BRC, the choroid was predominantly involved in

Fig. 2 Average FA score, ICGA score, dual FA-ICGA average (total posterior level of inflammation), and FA/ICGA ratio, by subtype of disease

	FA	ICGA	Dual FA-ICGA	FA/ICGA Ratio
OS	7.15 ±4.52	14.02 ±4.86	10.59 ±3.22	0.51
OT	6.19 ±4.11	13.56 ±7.15	9.87 ±4.39	0.46
BRC	16.06 ±6.46	18.88 ±3.65	17.47 ±3.40	0.85
VKH	4.58 ±2.11	20.83 ±7.55	12.71 ±3.52	0.22
Total	7.62 ±5.52	15.07 ±6.52	11.34 ±4.49	0.51

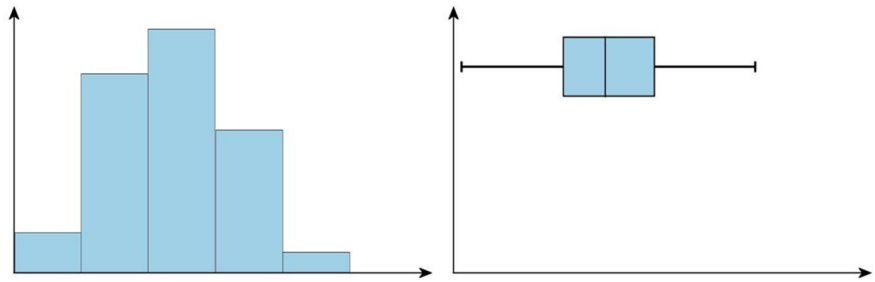

Fig. 4 Histogram showing all FA-ICGA scores, and boxplot showing median value as well as dispersion per quartile

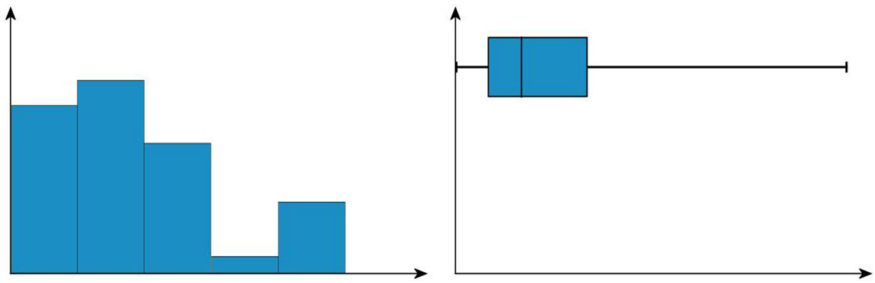

Fig. 5 Histogram showing all SUN-VH scores, and boxplot showing median value as well as dispersion per quartile

10/16 eyes (62.5%), the retina in 4/16 eyes (25%) and the 2 compartments were equally involved in 2 eyes (12.5%). Mean angiographic scores were 18.87 ± 3.65 for the choroid (ICGA) and 16.06 ± 7.0 for the retina. For VKH, the choroid was predominantly involved in all 12/12 eyes and angiographic scores were 20.83 ± 7.55 for the choroid and 4.58 ± 2.13 for the retina. Moreover, when analyzing the FA items in VKH, the pattern differed from the other 3 conditions that showed primary retinal inflammation (vasculitis), whereas the VKH FA scores were composed of signs of secondary retinal inflammation generated by severe underlying choroiditis, such as retinal hyperfluorescence due to subretinal fluid, and disc hyperfluorescence.

The histogram of all 128 FA-ICGA values, using a 10 points bin width, shows a symmetric, unimodal, Gaussian distribution of values. The boxplot, with whiskers from minimum to maximum, demonstrates even distribution of the values between its quartiles.

Only three dual FA/ICGA values out of the 128 eyes studied were more than two standard deviations from the mean score value for their respective disease. Hence, 97.7% of the values fall within two standard deviations, with the most reliable values (100% within 2 standard deviations) for VKH, and the weaker values (93.75% within 2 standard deviations) for BCR.

The inter-examiner variation showed that 8.4% of all scores had a discrepancy of more than one standard deviation (4.5), between two independent examiners.

SUN-VH score

When it comes to the SUN-VH score, only 22 of the 128 eyes (17%) showed a score of 2 or more, necessary for potential inclusion in a clinical trial. For OS, the mean SUN-VH score was 0.67 ± 0.66 with only 5/46 eyes (11%) having a score of 2 or more. Mean SUN-VH score for OT was 0.77 ± 0.72 with only 7/54 eyes (13%) having a score of 2 or more. For BRC, mean SUN-VH score was 1.56 ± 0.79, the highest of all four diseases, with 8/16 eyes (50%) having a score of 2 or more. For VKH, the mean SUN-VH score was 0.79 ± 0.72 with 2/12 eyes (17%) having a score of 2 or more.

The histogram of all 128 SUN-VH scores, using a 1 point bin width, shows a skewed, bimodal, non-normal distribution of values, and the boxplot, with whiskers from minimum to maximum, illustrates a range of values skewed towards zero, with an uneven distribution of the values between its quartiles.

For the SUN-VH, eight values out of the 128 eyes studied were more than two standard deviations from the mean score value. This means 93.75% of all values fall within two standard deviations. The test obtained more reliable values for BCR, with 100% results

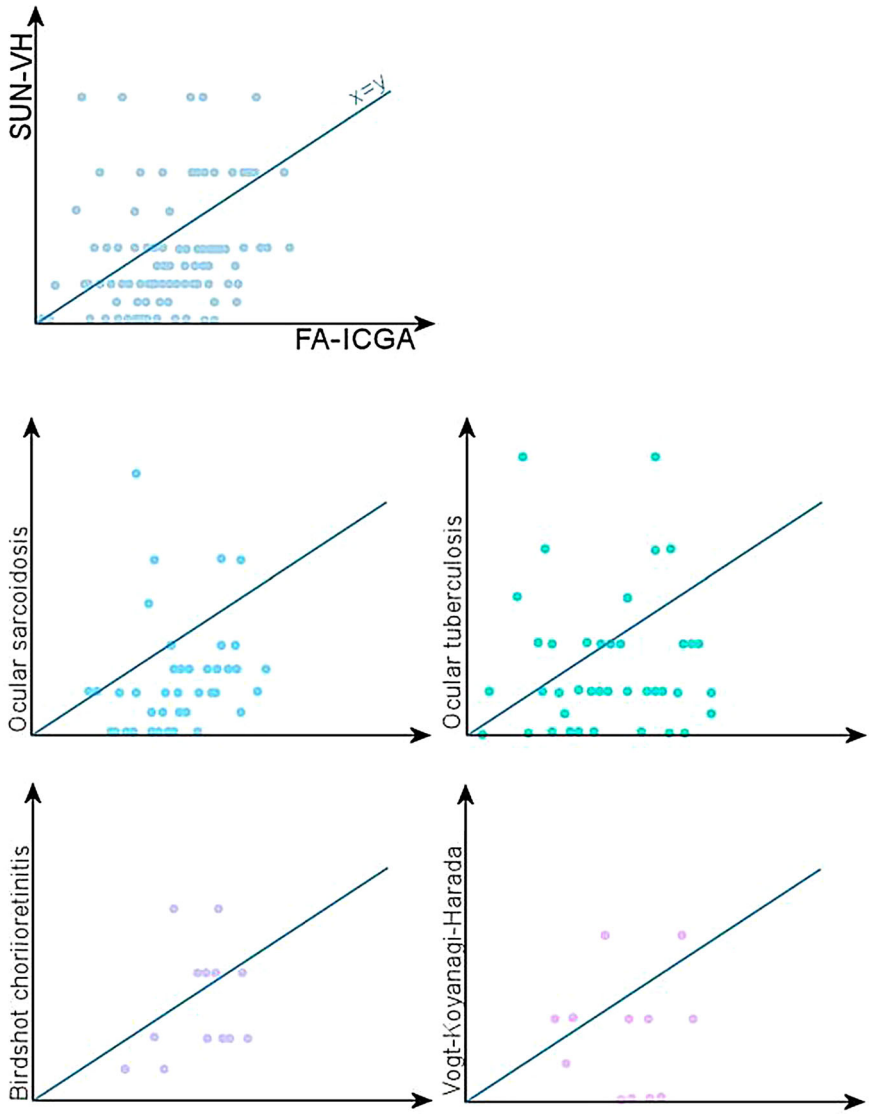

Fig. 6 *x = y function graph in which* x is the FA/ICGA score and y the SUN-VH score, for all diseases (top), for OS (middle-left), OT (middle-right), BRC (bottom-left) and for VKH (bottom-right)

within 2 standard deviations of the mean score value. The results were considerably less reliable for OS, with only 86.9% of the results being within two standard deviations of the mean.

The inter-examiner variation showed that 51.7% of all scores had a discrepancy of more than one standard deviation (0.76), between two independent examiners [18].

Comparative statistics

Simple comparison of the score value repartition around an x = y line, in which x is the FA/ICGA, and y is the SUN-VH score, shows that the scores are markedly skewed towards the abscissa. This demonstrates a stronger sensitivity of the FA/ICGA score, on average for all diseases, but more so for OS, and less so in the case of BCR.

Discussion

In this study, the dual FA/ICGA angiographic scoring system showed its potential in precisely determining in a numbered fashion the proportional contribution of retinal and choroidal inflammation in all subtypes of

stromal choroiditis entities, providing a more accurate and subtle clinical picture. OS and OT appear as predominantly stromal choroidal diseases. This was also the case for VKH with retinal involvement being minimal, while the proportion of retinal and choroidal involvement was relatively equal in BRC.

Detailed analysis of the individual score components also underlined that, in OS, OT and BRC, retinal and choroidal inflammation occurred concomitantly but were unrelated, while in VKH, inflammation exclusively started in the choroid with only secondary involvement of the retina following spill-over of choroidal inflammation. This shows that, not only that the FA/ICGA scoring provides a new way of assessing retinochoroiditis, but it also shows its full depth and potential in allowing fine analysis of the disease processes, which will undoubtedly have a major role to play in outcome measurement, follow-up, and management of such diseases.

On the other hand, a SUN-VH score has to be equal or superior to 2 to reach the threshold for clinical trial inclusion of patients, as this is required to allow for a two-step decrease of VH, the standard criterion used to determine significant improvement. This condition is only achieved in a very small proportion of patients. Relying on this score to recruit or assess patients in a stromal choroiditis-focused trial would lead to the exclusion of a vast majority of cases, and to the selection of a non-representative sample of patients, which would hence skew the outcome.

In this study, we performed several statistical evaluations of both tests' reliability and reproducibility and, in this regard, the following points have to be noted. The mean score value for FA/ICGA was substantially higher than that obtained with SUN-VH, showing that overall, the former is a much more sensitive test in assessing all subtypes of stromal choroiditis. There was much less discrepancy between the SUN-VH and the FA/ICGA score in BRC cases than in VKH, OS, and OT cases. This brings the new notion that the more predominantly choroidal a uveitis is, with a lower FA/ICGA ratio, the more the FA/ICGA score shows its strength, with much more significant values and wider gaps compared to the SUN-VH score.

The repartition of values obtained with the FA/ICGA method showed a normal distribution, with over 95% (97.7%) of its values sitting within two standard deviations of the average, a sign of test reliability. The SUN-VH score, however, has a non-normal distribution with less than 95% (93.75%) of values sitting within two standard deviations, which could be a sign of lack of reliability or reproducibility. Hence, we assessed the inter-examiner variability, and noted that over half of the SUN-VH scores (51.7%) marked by two independent examiners had a difference greater than 1 standard deviation versus only 8.4% for the FA/ICGA score. This shows that, despite a promising estimate of excess agreement beyond chance, the SUN-VH score only has mediocre inter-examiner repeatability, causing unwanted value dilution and dissemination. We can only speculate that this is due to the subjective nature of the test, while the FA/ICGA score's objective nature, involving tangible set criteria, is much more reproducible and, thus, reliable.

Clinical use and conclusion

This study highlights the precise measurement of global posterior inflammation achieved by a dual FA/ICGA scoring system in stromal choroiditis, and the weakness of the SUN-VH score for this specific group of diseases. As such, the FA/ICGA score should become one of the outcomes for future clinical trials studying posterior uveitis. In contrast, the SUN-VH scale, the qualitative and subjective criterion currently used in studies on posterior uveitis, appears wholly inadequate in stromal choroiditis, a major group of posterior uveitis entities. To allow meaningful and global assessment of posterior intraocular inflammation in stromal choroiditis, to improve follow-up, and to obtain statistically exploitable data for research, we recommend the use of dual FA & ICG angiography, in place of the currently recommended SUN-VH scaling system.

Compliance with ethical standards

Human and animal rights All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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