Inflammatory diseases and glaucoma

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(with the help of Dr. Sunaric-Mégevand for the paragraph on glaucoma evaluation devices)

1. Preamble: unprecedented precision in the appraisal and the management of patients and multimodal monitoring but reluctance of the medical community to use them.

The context in which glaucoma or hypertension in inflammatory diseases is taken care of today has to take into account the tremendous technical developments that have taken place in the last twenty past years or so. These advances are of course not limited to uveitic glaucoma or hypertension but are particularly beneficial in these complex cases where inflammatory and glaucomatous parameters have to be followed with the highest possible precision. Speaking only on the inflammatory aspect of the topic, we nowadays have at our disposal precise techniques to establish choroidal inflammation and its contribution to the inflammatory problem using indocyanine green angiography; ICGA, to monitor precisely the quality of the macula, using optical coherence tomography (OCT), to precisely measure macular retinal sensitivity using microperimetry, to precisely image the ciliary body and retro-iridal space, using ultrasound biomicroscopy (UBM), and finally to exactly and objectively measure intraocular inflammation, using laser flare photometry (LFP). The problem unfortunately is that, although most of these techniques are more than twenty years old, they are far from being used in routine practice showing the profound conservatism of the medical/ophthalmological community.

1a. New developments in assessing glaucoma.

Glaucoma is one of the fields where precision in assessing and monitoring patients has progressed most. Of course it is not my prerogative to develop this topic but for the sake of completeness let’s just cite some of the most relevant advances in assessing glaucoma including:

(1) Pachymetry to readjust intraocular pressure according to corneal thickness,

(2) IOP measurements independent of corneal structural properties (corneal thickness) using new devices such as the Pascal Dynamic Contour Tonometer,

(3) Irido-corneal angle assessment using dynamic gonioscopy and anterior chamber OCT as well as the UBM that gives additional information about the ciliary body and retro-iridal space,

(4) Measurement of structural alteration of the optic nerve and the Retinal Nerve Fibre Layer (RNFL) using OCT, HRT, GDxVcc,
(5) assessment of early functional alterations with the FDT (Frequency doubling technology perimeter) and SWAP (Short wave automated perimeter)

1b Indocyanine green angiography (ICGA)

ICGA allows to assess the inflammatory involvement of the choroid and the information gained by ICGA cannot be obtained by any other means. More than 50% of cases of posterior uveitis either start their inflammation in the choroid, have significant involvement of the choroid or even remain confined in an occult way to the choroid. What then is the contribution of ICGA to uveitic glaucoma? By showing unsuspected choroidal involvement, ICGA can be of major contribution in elucidating the diagnosis of uveitis and allow resolution of hypertension or glaucoma thanks to the introduction of specific therapy. We showed that in a group of patients with tuberculous uveitis, some of them having been diagnosed by ICGA, instauration of specific anti-tuberculous therapy reduced the mean pressure by 4.6 mmHg.[1]

The role of ICGA is well illustrated in a case of a Congolese patient presenting with a bilateral granulomatous hypertensive uveitis and a papillitis [Fig. 1a & 1b, left]. ICGA showed widespread occult involvement of the choroid [Fig. 1b, right] compatible with ocular tuberculosis and the diagnosis of presumed ocular tuberculosis was confirmed by a hyper-positive Mantoux test.

Figure 1a. Bilateral anterior uveitis with discreet granulomatous signs first erroneously interpreted as a HLA-B27 related uveitis against which speaks the bilaterality, the granulomatous KP and the hypertensive character.
Figure 1b. Angiographic work-up is characterised by disc hyperfluorescence shown by fluorescein angiography (left) but ICGA shows massif choroidal involvement (right) compatible with tuberculous uveitis confirmed by a hyperpositive Mantoux test. Resolution of uveitis and ocular hypertension was obtained after introduction of specific anti-tuberculous therapy.

1c Optical Coherence Tomography (OCT)

OCT allows to assess the quality of the macula in real time as often as necessary because it is a non-invasive and harmless procedure. It can be compared to tonometry in glaucoma that gives the immediate level of intraocular pressure. Like tonometry for glaucoma and laser flare photometry (LFP) for inflammation it gives the instantaneous state of the macula. As for the other two measurement devices it allows to instantly readapt therapy. Of course the quality of the OCT used plays an important role in uveitis because of the turbidity of the vitreous often present and uveitis centres should therefore be equipped with high-quality OCT instruments. We work preferentially with a Heidelberg instrument that represents a major gain of quality over other less performing OCTs especially in case of turbid media. Figure 2a is a scan taken with our OTI spectral OCT not allowing to have a sufficiently precise image in this patient with an infiltrated vitreous to show the cystoid macular oedema (CMO) which is clearly shown on the Heidelberg scan. [fig. 2b] The availability of OCT allows the use of prostaglandins analogues when absolutely necessary as the macula can be watched closely and these agents can be discontinued at the first signs of incipient macular oedema.

Figure 2a. The shape of the macula is insufficiently identified by an OTI spectral OCT in this patient with a turbid vitreous.
Figure 2b. The Heidelberg scan performed in the same patient gives a clear image of the macula showing CMO and in addition vitreoretinal traction is detected.

1d Microperimetry

Microperimetry is a functional test showing the sensitivity of the macular retina. It is more sensitive than 30 degree visual field analysis and even probably more sensitive than macular visual fields. It is however a subjective test and depends on the collaboration of the patient. Figure 3a shows the evolution of the visual field in a patient with a macular toxoplasmic retinochoroiditis seemingly showing a return to a quasi normal functional retina after treatment. Microperimetry however shows a more important persisting deficit of retinal sensitivity than is apparent from visual field testing. [fig. 3b]
1e Ultrasound biomicroscopy (UBM)

Evaluation of the inflammatory involvement of the iris stroma and retroiridal face, ciliary body, pars plana and retroiridal vitreous is sometimes important. These structures are not readily accessible with routine examination methods. Evaluation of the retrolenticular and retroiridal space is even more important when no visual access to the posterior segment is possible because of opaque media. In such cases ultrasonography is the method of choice. B-scan ultrasonography has become an essential and well-established device to help diagnose and manage ocular and orbital disorders. More recently high-frequency ultrasonography has been introduced and made available to clinical practice. The method has been named ultrasound biomicroscopy (UBM) and is based on high-frequency transducers incorporated into a B-mode clinical scanner. This technology allows quasi-histological sections up to 3-6 mm in depth to be obtained in vivo, giving access to structures in the anterior part of the posterior segment that cannot be visualised otherwise or that are inaccessible because of opaque media. The method has been shown to be valuable in inflammatory pathologies of the anterior part of the ciliary body and retroiridal space. In some cases UBM is useful in determining the origin of intraocular hypertension. It is especially important in planning surgery in uveitis hypertensive eyes with ciliary body pathology as surgical intervention might be contraindicated in cases where hypertension is due to angle closure and where the ciliary body is completely atrophic. Figure 4 shows a classical 10 Hz echography image of the posterior segment with a dropped lens in a patient presenting an ocular hypertension with values between 30 and 40 mmHg (left picture) On the right the UBM picture shows a closed angle with a completely atrophic ciliary body that lets anticipate ptosis bulbi in case of filtering surgery.

Figure 4. Phacodropping causing secondary uveitis with secondary glaucoma with a completely atrophic ciliary body.
1f. Laser flare photometry (LFP)

Laser flare photometry (LFP) is to uveitis what tonometry is to glaucoma. It allows to evaluate the level of inflammation at any given time. It therefore allows to measure the exact level of inflammation and to plot it against IOP values and other parameters. In 1959, a standardization system for the evaluation of intraocular inflammatory activity in uveitis was established and has been almost universally used for more than 40 years. [2,3] In 2004 a panel of uveitis specialists that convened to establish new universal criteria for the standardization of uveitis nomenclature (SUN) re-adopted this grading system essentially unchanged despite the fact that Laser flare photometry (LFP), a precise new technology for the grading of intraocular inflammation had been available for more than 20 years. [4] Despite these efforts of standardization, the assessment of inflammation (aqueous cells and flare) still remains subjective with large intra-observer and inter-observer variations. Aqueous flare and cells are the most useful parameters to evaluate the progression or regression of inflammation in the anterior segment. Because anterior chamber cells could be quantified to a certain extent, this was considered to be the preponderant parameter in anterior inflammation by uveitis specialists. [5] Flare was considered less useful because it could not be evaluated as accurately as cells. The slit-lamp assessment of both flare and cells in the aqueous humour is based on the same optical principle of recording back scattered-light particles (photons) from a light beam directed into the anterior chamber. [6] Laser flare photometry (LFP), a new technology commercially available since 1989, is based on the same principle as slit-lamp flare evaluation, measuring back-scattered light from protein particles in the anterior chamber. [7] It differs however from slit-lamp flare evaluation in several crucial aspects. The light source (incoming light) in laser flare photometry is a laser beam, by definition monochromatic, emitting a constant quantity of photons over time, whereas the incoming light in slit-lamp flare evaluation is polychromatic and subject to fluctuations. In slit-lamp flare evaluation the detector is the human eye and the data are analysed by the human brain, whereas in LFP the detector is a photodetector/photomultiplier and the data are analysed by a computer. This represents a tremendous gain of sensitivity, making flare the only inflammatory parameter that can be quantified to date. The extent of sensitivity gain over the classic slit-lamp flare evaluation becomes evident when considering the two scales. A scale ranging from 1 to 4 in slit-lamp flare evaluation compared to a scale ranging from 4 photons/millisecond (ph/ms, the normal flare value in a non-inflamed eye) to values as high as 1000 ph/ms in laser flare photometry (LFP) indicate the difference of sensitivities. [8] Precise follow-up of inflammation is now possible not only for flare levels that are clinically apparent but also in low or subclinical flare states on one side and very high flare states on the other side, two situations where the human eye is absolutely unable to measure flare variations. [9] Laser flare photometry has become the standard method in evaluating post-surgical anti-inflammatory therapy such as in post-cataract inflammation. [10,11,12] It has also been shown to be reliable to monitor therapy and predict inflammatory recurrences in posterior uveitis when a sufficient level of associated blood aqueous barrier disruption (flare) is present. [13] In a recent article we showed laser flare photometry to be superior to slit-lamp cell evaluation to monitor intraocular inflammation. [14] The problem is that LFP has been discarded by one of the nation most influential on medicine practice in the world refusing to practice common sense based medicine (CSBM), which slowed down the acceptance of this obviously unavoidable methodology. Figure 5 shows two cases of HLA-B27 related uveitis both having low intraocular pressure. The first case (red line on graph) presents with an inflammation of more than 400 ph/ms and LFP shows that it readily responds to classical corticosteroid drops. Responds to steroids is associated with an increase of pressure in this patient. The second patient (yellow line on graph) is not responding to standard therapy and flare is still high (while pressure remains low) after 48 hours and only an orbital floor injection of aqueous steroids is bringing inflammation down. The naked eye, using the slit-lamp could never have detected the differential response to therapy in these patients.
1g. Multimodal monitoring in uveitic glaucoma (figure 6)

The monitoring devices that are at our disposal nowadays give us control upon the main glaucomatous and inflammatory parameters allowing to immediately reorient and adapt therapeutic intervention in a precise fashion and therefore fundamentally changed our management of such complex cases. **Figure 6** shows a composite slide on the long-term evolution of a severe case of ocular sarcoidosis. The patient had been under therapy previously and presented on November 6, 2007 with a severe recurrence after having discontinued all therapy.

Vision was down to 0.05 OD and 0.4 OS. Inflammation was elevated with values of 60 ph/ms OD and 41 ph/ms OS. IOP was low with values of 9 mmHg OD and 11 mmHg OS. Severe cystoid macular oedema (CMO) was present (top left set of parameters). High-dose systemic corticosteroids were started concomitant to systemic azathioprine (Imurek®, 150 mg then increased to 175 mg) together with Pred-Forte® QID as well as Cosopt® preventively. Two weeks later VA was up to 0.2 OD and 0.6 OS; flare was down to 26 ph/ms OD and 21 ph/ms OS, CMO improved but IOP was up to 30 mmHg OD and 48 OS (second set of images to the right). PredForte® was stopped and a prostaglandin analogue was introduced. The consequence was an increase of inflammation to 42 ph/ms OD and 33 ph/ms OS with normalisation of pressure and a macula in control without increase of CMO. Two months later vision had decreased to 0.1 OD and 0.5 OS, inflammation had increased to 54 ph/ms OD and 29 ph/ms OS and CMO had recurred OD while IOP was normal. Travatan® was then stopped with reduction of the CMO, drop of inflammation to 36 mmHg OD and 25 ph/ms OS and normal pressure values. Another one month later inflammation recurred with a decrease of VA to 0.05 OD and 0.5 OS, flare values were at 47 ph/ms OD and 38 ph/ms OS and recurrence of bilateral CMO was seen, while pressure remained normal. Immunosuppression was changed to Myfortic®. Two years later the situation was well controlled with minimal inflammation, normal pressure and satisfactorily OCTs under Myfortic monotherapy. This case illustrates well the precision and good reactivity obtained by modern multimodal monitoring to adapt therapeutic intervention.
2. Glaucomatous/hypertensive situations in uveitis and their management. (angle open)

At least 3 main types of hypertensive/glaucomatous situations occur in inflammatory diseases or uveitis and therapeutic measures should be taken and adapted accordingly.

2a. Short-term IOHT in uveitis of limited duration

There are at least 3 current uveitis entities that fall into this category. The first is HLA-B27 uveitis that initially presents with hypotension when it is severe or normal pressure when it presents with moderate severity. Increase of pressure occurs usually a few days later and it can mostly be ascribed to topical or periocular steroid therapy. This type of situation can usually be managed simply using intraocular pressure lowering drops ± oral acetazolamide. There is usually no need to use prostaglandin analogues. Hypotensive therapy is necessary until corticosteroid drops can be tapered or until the effect of depot peri-ocular injections Kenacort® (triamcinolone) used when there is posterior involvement, is vaning. Functional consequences do usually not occur.

The second current short-term hypertensive complication of uveitis currently diagnosed in our Swiss setting occurs in toxoplasmic retinochoroiditis as this is the most frequent posterior uveitis found in our area. Toxoplasmic retinochoroiditis can present with an associated anterior granulomatous uveitis which is very often producing IOHT. Treatment is usually limited to pressure lowering drops excluding prostaglandin analogues but sometimes needs the association of oral acetazolamide. IOHT is self-limited and depends on the efficiency of the specific anti-toxoplasmic therapy. Of course, in addition to the inflammatory mechanisms causing hypertension there can be an additional contribution of the systemic and local use of corticosteroids necessary in toxoplasmic retinochoroiditis. Functional consequences of hypertension is difficult to sort out as the retinochoroiditis is also causing visual field loss. (Figure 7a & 7b)
Thirdly, herpetic uveitis, expressing itself very often as an anterior granulomatous uveitis, is associated in a large proportion of cases with IOHT, which even is considered as a diagnostic criterion. In most cases IOHT can be controlled with medical anti-glaucoma therapy. In contrast to the two previous situations here above, pressure peaks are sometimes higher and prostaglandin analogues may have to be used although they could very hypothetically favour herpes recurrence. The mainstay therapy consisting of topical low-dose corticosteroids (dexamethasone 0.1%) associated with systemic and topical antiviral therapy mathematically will get this uveitis under control.
control. Anti-hypertensive therapy is needed during this process and usually can be stopped once the herpetic and autoimmune process are under control. In some cases patients fall into situation 3 (see hereunder) where pressure gets out of control and deep sclerectomy has to be performed as illustrated in the case described hereunder. (figures 8a & 8b & 8c)

Figure 8a

**Situation 3 : Mr. Philippe G., 33 years old (1)**

- Chronic uveitis treated classically with a Maxidex® (0.1% dexamethasone)
- Along the years episodes become more numerous and therapy is needed for more than 6-8 months per year.
- Pressure is increasing steadily and has reached 44 when we see the patient
- What should be done’

Figure 8b.

**Case 3 : Mr. Philippe G., 33 years old (3)**

- What is the diagnosis?
- What therapy should be given?
  - oral antiviral therapy
  - topical dexamethasone 0.1% or similar
  - relay with topical antiviral after 1-2 months
  - progressive tapering of therapy
  - Over 1 year (cave recurrences)
Figure 8c.

Case 3: Mr. Philippe G., 33 years old (6)

- Keratouveitis is under control but pressure goes up and remains between 30 and 52 mmHg despite maximal anti-glaucomatous therapy and despite tapering and discontinuation of steroid drops
- Disc excavation C/D = 0.9
- Deep sclerectomy is performed
- Pressure stabilised around 12 mmHg

When herpetic keratouveitis is not controlled mathematically as indicated here above we have to think of cytomegalovirus anterior uveitis and anterior chamber puncture has to be performed to search for CMV DNA by polymerase chain reaction and antiviral therapy has to be changed from valacyclovir to valgancyclovir.

In all these situations there may be high pressure peaks that need the sporadic use of osmotic agents (glycerotone®) to cut these pressure peaks.

2b. IOHT in long-term intra-ocular inflammation (chronic uveitis)

Uveitis entities with a prolonged course are often associated with IOHT directly due to uveitis factors but also to the use of topical, periocular and/or systemic steroids that goes along with this type of uveitis. This IOHT is often occurring in granulomatous uveitis including sarcoidosis and tuberculosis but also in non-granulomatous chronic uveitis such as intermediate uveitis especially of the pars planitis type. In that situation the attempt should be done to control IOHT by all medical means at our disposal while waiting for the control of inflammation by IST (inflammation suppressive therapy). IST should be devoid of corticosteroids but consist of “old” immunosuppressants known for their good tolerance and limited side-effects such as azathioprine (Imurek®) or by the increasingly used “new” immunosuppressants such as mycophenolate mofetyl (Myfortic®) or immunomodulators such as anti-TNFα or interferon-α. The solution of IOHT is usually achieved by the control of inflammation. (Figure 6)

2c. Non controllable "Fukushima" type of IOHT/glaucoma

At any stage of follow-up the situation can present where things go out of control and pressure becomes medically uncontrollable. This situation is well illustrated in the case of the patient presented in figure 8. The conditions where such an evolution is occurring include herpetic uveitis, anterior CMV uveitis and Fuchs’ uveitis as well chronic granulomatous uveitis. Fuchs’ uveitis is a particular situation regarding IOHT. In about 80% of Fuchs’ uveitis cases, IOHT does not develop and pressure in the Fuchs eye is nearly always lower than in the normal eye. In 17-20% of Fuchs patients, IOHT develops and is characterised by strongly fluctuating pressures very difficult to
control medically. A large proportion of cases go on towards situation 3 of uncontrollable pressure and need surgery.

2d. Mixed situations

Among the chronically evolving uveitis cases where IOHT is ultimately mastered by progressive control of inflammation some cases can suddenly present an unsuspected evolution towards uncontrollable pressure that can only be resolved by surgical intervention (deep sclerectomy). This is illustrated in figure 9. IOP was brought under control by a progressive reduction of the level of inflammation from 177 to 42 ph/ms on the right and from 244 to 64 ph/ms on the left following immunosuppressive therapy. At some point pressure went up again even in the absence of corticosteroid use. Evolution towards uncontrolled pressure is explained by a still too high inflammation allowing clogging of the trabecular meshwork. This indicates that zero tolerance of inflammation has to be aimed at.

Figure 9a.

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<th>1d. Mixed situations – case 1 (a)</th>
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<tr>
<td>54 y-old lady</td>
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<tr>
<td>Bilateral inflammation / ocular sarcoidosis</td>
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<tr>
<td>Cataract operation OD w/o prophylactic trifluridine</td>
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<tr>
<td>VAODOS = 0.1/0.4</td>
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<tr>
<td>Flare OD/OS : 177/244 ph/ms</td>
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<tr>
<td>IOP OD/OS : 224/25 mmHg</td>
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<tr>
<td>Vitritis: ++ OD</td>
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<tr>
<td>Secondary cataract OD / + 360° synechiæ OS</td>
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<tr>
<td>Fundus: ➔ photo</td>
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<td>FA ➔</td>
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<tr>
<td>TTT: Stretch Tenon’s Keracton® OU</td>
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<tr>
<td>Immurex® 175 mg</td>
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<td>Pred Forte®: 10X</td>
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<td>Cozipad®</td>
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<td>Dilating drops</td>
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<td>Leter Diamox®</td>
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Figure 9b.

<table>
<thead>
<tr>
<th>1d. Mixed situations – case 1 (b) Evolution 1</th>
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<tr>
<td>Evolution 1 after 9 months of treatment:</td>
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<tr>
<td>VA OD/OS = 0.8/0.4</td>
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<tr>
<td>Flare OD/OS : 428/34 ph/ms</td>
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<td>IOP OD/OS : 21/21 mmHg</td>
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<td>Vitritis: ++ OD</td>
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Evolution 2: after 2 years:
VA OD/OS = 0.8/0.5
Flare OD/OS : 48/37 ph/ms
IOP OD/OS : 29/26
Glycerol + addition of Travoprost
 ➔ Nothing helps any more OS
 ➔ Combined cataract + deep sclerectomy

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3. What has changed in the appraisal of uveitic glaucoma, summary and practical indications.

3a. We have performing monitoring capacities that are unprecedented and that allow us to quickly and, most of the time, effectively adapt therapy.

3b. Appraisal and work-up of uveitis has improved:
   - specific diagnosis of uveitis is reached in up to 70% of cases
   - infectious and non infectious uveitis are easily sorted out
   - even if diagnosis is not found, monitoring capacities allow to determine the behaviour of a given uveitis case.

3c. Distinguish between the 4 presentation modes of uveitic IOHT including (1) short term IOHT in uveitis of limited duration (B27, toxo, herpes), (2) IOHT in chronic uveitis, (3) uncontrollable episodes IOHT/glaucoma and (4) mixed situations, and take appropriate therapeutic steps accordingly.

3d. IST (inflammation suppressive therapy) has improved, getting away from the long-term use of steroid therapy and increasingly and increasingly using immunosuppressants comprising new potent, well-tolerated substances
   ⇒ IOHT preventing constellation

3e. Surgical techniques have improved (deep sclerectomy) taking away from us the fear to decide upon performing surgery. On the other hand these new performing surgical techniques that avoid post surgical hypothalamy give us, paradoxically in a supposedly steroid free uveitis world, the freedom to use as much steroids as wished, especially in the periocular subTenon’s steroid injection mode.
References