Intra-ocular inflammation: Industry view

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Outline

- Target population
- Endpoints
- Comparators
- Clinical trial design and duration
- Managing heterogeneity and rescues

Target population

- Chronic non-infectious uveitis is an orphan indication affecting < 4.8 in 10,000 persons in the EU[1]
- Heterogeneous
- Treatment (EU)
  - Steroids
  - Ciclosporine
  - Off-label use of immunosuppressives

[1]EMA 3March2010 EMA Public summary of opinion on orphan designation for Novartis antibody to IL-17A.

Target population: "Lumping"

Emphasis on location and tempo of inflammation

TABLE 1. The SUN* Working Group Anatomic Classification of Uveitis

Type	Primary Site of Inflammation†	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

*SUN = Standardization of uveitis nomenclature.

†As determined clinically. Adapted from the International Uveitis Study Group anatomic classification in reference 1.

TABLE 2. The SUN* Working Group Descriptors of Uveitis

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

*SUN = Standardization of uveitis nomenclature.

SUN working group. Am J Ophthalmol 2005;140:509-5

Target population: “Splitting”

Specific entities or characteristics

- Behcet’s disease
  - Recurrent attacks of occlusive vasculitis, systemic
- Vogt-Koyanagi-Harada syndrome
  - Serous retinal detachments, systemic
- Birdshot retinochoroidopathy
  - Electroretinographic abnormalities
- Scleritis
  - Intra-ocular inflammation may be secondary

Target patient population

A key clinical issue is steroid side effects

- Steroids are effective
  - Eyedrops
  - Peri- or intra-ocular injections
  - Oral or intravenous
- Challenge is managing steroid side effects with prolonged or recurrent

Table 3-1 Medicinal Products Authorised in the European Community for treatment of uveitis

Tradename, active ingredient/generic	Holder of marketing authorisation	Authorised indication
Calcort® 6 mg tablets, deflazacort	Sanofi-Aventis	A wide range of conditions treated with glucocorticoids, including **uveitis**, optic neuritis
Deltacortril® 2.5 mg and 5mg gastro-resistant tablets, prednisolone	Alliance Pharmaceuticals	A wide range of conditions including **posterior uveitis**, scleritis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease
Medrone tablets 2 mg, 4 mg, and 16 mg, methylprednisolone	Pharmacia	A wide range of conditions including anterior uveitis (iritis, iridocyclitis) **posterior uveitis**, and optic neuritis
Minims Dexamethasone 0.1% w/v Eye Drops, dexamethasone sodium phosphate	Bausch & Lomb	Non-infected, steroid responsive, inflammatory conditions of the eye
Dexsol 2 mg/5 ml oral solution, dexamethasone sodium phosphate	Rosemont Pharmaceuticals	A wide range of conditions including anterior and **posterior uveitis**, optic neuritis, chorioretinitis, iridocyclitis, temporal arteritis, orbital pseudotumour
Ciclosol® 25 mg, 50 mg, 100 mg capsules, ciclosporin	Ecosol AG	Conditions including **uveitis** (endogenous)
Sandimmun Neoral® 100 mg capsules, ciclosporin	Novartis	Conditions including **uveitis** (endogenous)

2011 Ozurdex CHMP assessment

Endpoints

Endpoint		Comment
Visual acuity	•Proportion with ≥ 15 letter change •Mean change from baseline in VA score	≥10 letter change may be clinically meaningful
Anterior chamber	•Clearing (0) •Improvement (2-step) • Worsening (2-step or change from 3+ to	Scale 0, 0.5+, 1+, 2+, 3+,
Vitreous haze		Ozurdex precedent
Sparing of steroid therapy	•Elimination of topical or ocular injection therapy •Decrease to ≤10 mg prednisone equivalent/day[1]	
Macular edema	Reduction in retinal center subfield thickness of ≥20%[2]	Baseline thickness ≥260 µm
Recurrence	Fewer episodes separated by periods of inactivity w/o treatment ≥ 3 mos[1]	Alternative is time to recurrence
Remission	Inactive disease for ≥3 mos after discontinuing all treatment[1]	

[1]SUN working group. Am J Ophthalmol 2005;140:509-51
[2]Sugar et al. Am J Ophthalmol 2011 (ePub in press)

Clinically meaningful threshold for change in uveitic macular edema evaluated by OCT is 20%

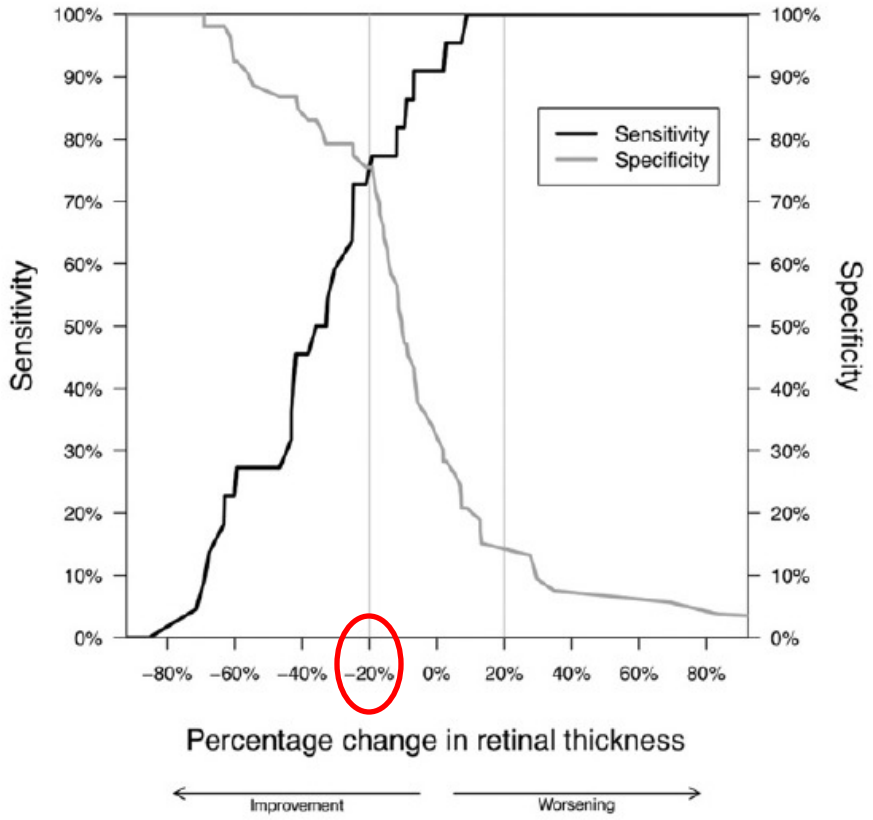


FIGURE 2. Graph showing the sensitivities and specificities associated with different thresholds of percentage change in retinal thickness (measured by optical coherence tomography at the central subfield) for identifying an increase greater than 10-letters in visual acuity in eyes with uveitic macular edema.

TABLE 4. Estimates of the Sensitivity and Specificity of a 20% Improvement in Retinal Thickness Measured by Optical Coherence Tomography at the Central Subfield for Identifying Clinically Important Changes in Visual Acuity in Eyes with Uveitic Macular Edema (Defined as Retinal Thickness ≥240 μm)

Change in Visual Acuity (Letters)	Sensitivity (95% CI)	Specificity (95% CI)
>5	71% (55% to 89%)	88% (75% to 97%)
>10	77% (60% to 95%)	75% (62% to 86%)
≥15	77% (50% to 100%)	68% (54% to 80%)

CI = confidence interval.

Bootstrap estimates of the 95% confidence intervals are provided in parentheses.

Sugar et al. Am J Ophthalmol 2011 (ePub in

Potential endpoint for Immunosuppression: Immunosuppressive load

Nussenblatt et al · Subcutaneous Daclizumab for Uveitis

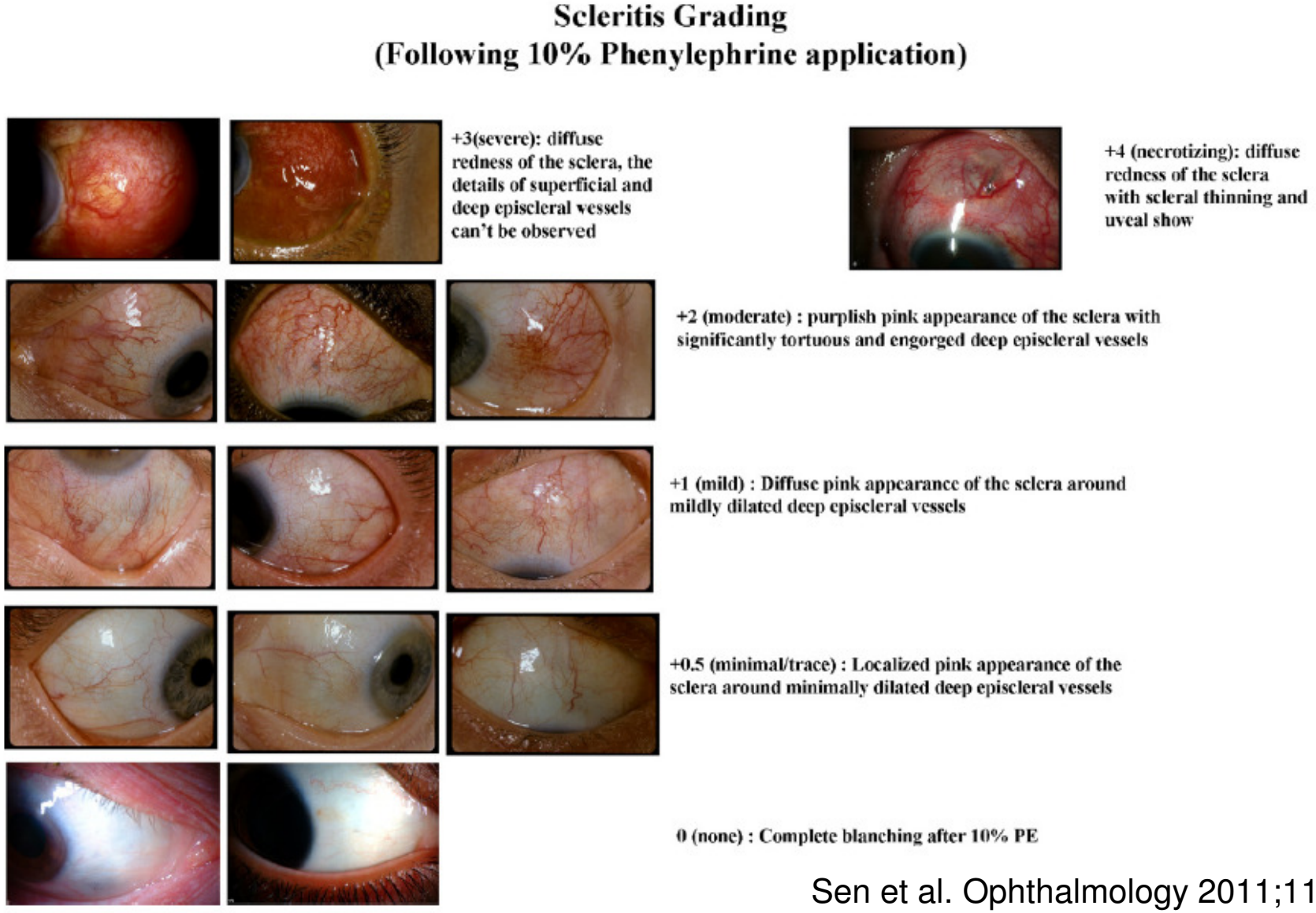
Table 2. Grading Scheme Used to Tabulate Immunosuppression Load and Categorize Changes in Treatment Regimen between Visits

	Immunosuppression Grade, Based on Dose in mg/kg/day (or per Week if Dosed Weekly)									
Medication	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Prednisone	0	<0.15	0.15–0.30	0.31–0.45	0.46–0.60	0.61–0.75	0.76–0.90	0.91–1.05	1.06–1.20	>1.20
Cyclosporine	0	<0.75	0.75–1.50	1.51–2.25	2.26–3.00	3.01–3.75	3.76–4.50	4.51–5.25	5.26–6.00	>6.00
Azathioprine*	0	<0.25	0.25–0.50	0.51–0.75	0.76–1.00	1.01–1.25	1.26–1.50	1.51–1.75	1.76–2.00	>2.00
Mycophenolate	0	<10	10–20	21–30	31–40	41–50	51–60	>60	—	—
Methotrexate	0	<0.05	0.05–0.10	0.11–0.15	0.16–0.20	0.21–0.25	0.26–0.30	0.31–0.35	0.36–0.40	>0.40
Cyclophosphamide	0	<0.25	0.25–0.50	0.51–0.75	0.76–1.00	1.01–1.25	1.26–1.50	1.51–1.75	1.76–2.00	>2.00
Chlorambucil	0	<0.025	0.025–0.050	0.051–0.075	0.076–0.100	0.101–0.125	0.126–0.150	0.151–0.175	0.176–0.200	>0.200

Dose ranges are for the average in mg/kg/day, except for weekly doses of methotrexate, which are measured as mg/kg/week. Grade 1 is assigned to any administered dose that is less than the designated limit.
*No patients in this study enrolled while receiving azathioprine.

Nussenblatt et al. Ophthalmology 2005;112:764-770

Potential endpoint for Scleritis: Scleritis grade



Sen et al. Ophthalmology 2011;118:768-7

Figure 1. Scleritis grading system. Standardized digital photographs of scleritis of varying severity. Graders used this illustration as reference photographs in session 2. PE = phenylephrine.

Comparators
Current status quo

- Typically steroids – Topical, periocular, intravitreal, or systemic
  - Challenge: Standard of care includes off label use of many medicines
- Basic paradigms
  - Control active disease – New or recurrent
  - Reduce steroid/immunosuppresive dose(s) required to control disease

Clinical trial design and duration

- Design
  - Disease control
    - Head to head (vs standard of care, usually steroids)
  - Steroid (or immunsuppressive)-sparing
    - [Drug + Steroid] vs [Placebo + Steroid] → Steroid taper
- Duration
  - Safety
    - New indication for previously approved drug : ≤ 1 year
    - New molecular entity: 1 year
    - Recommendations for sustained-release formulations will vary
  - Efficacy – Depends on type of uveitis
    - Front of the eye inflammation: 3 months
    - Back of the eye inflammation: 6 months
    - Special cases, e.g. Behcet's, Vogt-Koyanagi-Harada: 1 year

Managing heterogeneity

- Understanding of
  - Disease pathogenesis
  - Mechanism of action of drug
  - Responsive subpopulations
- Aspiration: Incorporating such understanding into phase 3 design
- Challenge: Knowledge gaps

Handling rescued patients

- Endpoints of recurrence or remission would be based on rescues
- For other endpoints
  - Dichotomous endpoint, e.g. Responder analysis
    - Score rescue as failure
  - Continuous endpoint, e.g. VA score
    - Intent to treat with last observation carried forward
      - Sensitivity analysis using per protocol population

Summary

- Target population
  - Dealing with heterogeneity: Lumping vs splitting
- Endpoints
  - Multiple endpoints available
- Comparators
  - Typically steroids but may include off label use of medicines
- Clinical trial design and duration
  - Disease control vs steroid (immunosuppressive)-sparing
  - Duration may depend on type of uveitis and whether or not the drug is a new molecular entity. Sustained release handled case by case.
- Managing heterogeneity and rescues
  - Understand biology - Challenge is knowledge gaps
  - Rescues can be scored as endpoints themselves or be managed with selection of population and imputation method as appropriate