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Outcome measures in juvenile X-linked retinoschisis: A systematic review

John R. Grigg [1,2,3] · Claire Y. Hooper[1,2] · Clare L. Fraser[1,2,3] · Elisa E. Cornish[1,2,3] · Peter J. McCluskey[1,2,3] · Robyn V. Jamieson[1,2,4]

Abstract

X-linked retinoschisis (XLRS) is a leading cause of hereditary juvenile macular degeneration in males resulting in significant vision impairment. Outcome measures to monitor disease progression or therapeutic interventions have evolved with technology. A systematic review was undertaken to evaluate outcome measures for XLRS. Inclusion criteria were all publications examining outcome measures for natural history studies or following an interventional approach for patients with XLRS. Studies which did not present follow-up data were excluded. We searched medical databases including CENTRAL, Ovid Medline, pre-Medline and ahead of Print up to February 2019. Two authors independently assessed the risk of bias. Twelve studies meet the inclusion criteria with four prospective and eight retrospective case series. Five series were natural history observational studies and seven were interventional series using either topical or systemic carbonic anhydrase inhibitors. Visual acuity (VA) declined very slowly in the natural history studies equivalent to 0.22–0.5 letters per year. Five of the six interventional studies showed an improvement in VA and four a reduction in spectral domain optical coherence tomography (SD-OCT) parameters for central macular thickness (CMT). The full-field electroretinogram identified the 30-Hz latency as a further parameter to monitor function. VA was the measure most likely to show a statistically significant outcome. How functionally meaningful this is, requires further evaluation. CMT SD-OCT outcomes are variable depending on cystic changes. More refined measures are required to better correlate structure with function.

Introduction

X-linked retinoschisis (XLRS) is the leading cause of hereditary juvenile macular degeneration in males with, an estimated prevalence ranging from 1 in 15,000 to 1 in 30,000. It accounts for ~5% of all childhood-onset inherited retinal dystrophies [1]. It is caused by mutations in the RS1 gene encoding retinoschisin resulting in schitic changes traversing the inner retinal layers [2]. Clinical findings include bilateral, cyst-like macular changes and areas of peripheral bullous elevation. Vision is affected progressively with age, leading to poor central vision after the fifth decade of life [3]. There is a wide genotype–phenotype variability within families and with age as the schisis degenerates to atrophy [4–10]. Identifying the causative mutation is helpful in confirming diagnosis and genetic counselling. Although the severity of the RS1 mutation (e.g., missense vs. non-sense) may affect the phenotype and rate of early vision loss, our current understanding does not enable prognosis to be predicted [5, 11].

Treatments to date have had limited impact on vision. The main therapies assessed through clinical trials have been carbonic anhydrase inhibitors which aim to reduce the retinal cystic changes. Advances in genomic medicine have enabled gene therapy-based approaches to be

✉ John R. Grigg
john.grigg@sydney.edu.au

1 Discipline of Clinical Ophthalmology and Eye Health, Faculty of Medicine and Health, Save Sight Institute, 8 Macquarie Street, Sydney, NSW 2001, Australia

2 Eye Genetics Research, The Children's Hospital at Westmead, Save Sight Institute, Children's Medical Research Institute, University of Sydney, Sydney, NSW, Australia

3 Sydney Eye Hospital, Macquarie Street, Sydney, NSW, Australia

4 Disciplines of Genetic Medicine and Child and Adolescent Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

applied to inherited retinal dystrophies. Genetic therapies for XLRS are now a real possibility with the commencement of a phase one trial evaluating the safety and efficacy of rAAV-hRS1 in trial patients [12, 13].

With the development of specific gene-based therapies, the question arises as to when the best time is to intervene. XLRS has a bi-modal presentation. The most frequent presentation coincides with school screening or commencement of school, followed by minimal or slow progression until the fourth or fifth decade when central atrophy intervenes [3, 14–17]. Eksandh et al. reported that slow progression may not always be the natural history. In their review of full-field electroretinogram (FFERG) outcomes in children <10 years of age, they reported two children with initially normal FFERG b-wave amplitudes which became abnormal over 2 years [18]. The second less common presentation is with strabismus, vitreous haemorrhage, nystagmus or reduced visual acuity (VA) due to peripheral schitic complications frequently before the age of 2 years. The prognosis in these patients is worse with vitreous haemorrhage and retinal detachment frequently occurring before the age of 11 years [19]. Intervention before foveal schisis degenerates into atrophy has been recommended [17, 20]. It remains unclear which factors affect the time course of developing outer retinal atrophy [3, 8, 21].

Clinical trials seek to evaluate whether an intervention is safe and effective. This is determined by comparing the effects of interventions on outcomes chosen to identify the beneficial or harmful effects. For the majority of XLRS patients the condition progresses slowly, particularly between the ages of 10 and 50 years, so it is imperative that any clinical test used to detect disease progression be characterized by a high level of specificity [22].

The objective of this review was to synthesize the best available evidence regarding monitoring the natural history of XLRS and outcome measures in therapeutic trials in patients with XLRS. In particular, the role of functional tests, structural assessments and patient-related outcome measures (PROMs) were considered in this review. This information will inform prospective trials with novel therapeutic agents.

Methods

Protocol and registration

This systematic review is assessing published outcomes in XLRS. To date there are no published protocols for reviewing outcomes in XLRS. There are a number of registered clinical trials either interventional [12, 23] or observational [13, 24] which incorporate outcome measures in XLRS. The PRISMA guidelines for systematic reviews were used [25]. This systematic review has been registered with PROSPERO at https://www.crd.york.ac.uk/PROSPERO/.

Eligibility criteria

Inclusion criteria for this systematic review involved all publications that examined the outcome measures for natural history studies or following an interventional approach for patients with XLRS.

The exclusion criteria were: studies reporting three or less patients, studies which did not present follow-up data or studies reporting sub-phenotype, e.g., bullous retinal schisis. The exclusion criteria were chosen to ensure that repeatability of performance with the outcome measures could be assessed. More than three patients in the study were chosen to improve statistical assessment and minimize chance assessment. Excluding sub-phenotypes enables outcomes most relevant for novel therapeutic trials.

Search methods for identifying studies

Two authors (JRG and CYH) independently searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2019), Ovid MEDLINE, Ovid MEDLINE (R) In-Process and Other Non-Indexed Citations, Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline (R) Daily, Ovid MEDLINE and Versions (January 1946 to February 2019) (Supplementary Appendix 1). EMBASE (January 1980 to February 2019), EBM Reviews—Cochrane Database of Systematic reviews 2006 to June 2018, EBM reviews—ACP Journal Club 1991 to February 2019 EBM reviews—Database of Review of Effects 1st Quarter 2019, EBM reviews—Cochrane Clinical Answers February 2019 EBM Reviews—Cochrane Central Register of Controlled Trials February 2019, EBM Reviews—Cochrane Methodology Register 4th Quarter 2018, EBM Reviews—Health Technology Assessment 4th Quarter 2018, EBM Reviews—NHS Economic Evaluation Database 1st Quarter 2018 Embase Classic + Embase 1947 to February 2019, ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en).

We pre-specified the following investigation strategies for evaluation: structural assessment: optical coherence tomography (OCT), fundus autofluorescence, fundus or retinal photography; functional assessment: VA, perimetry static or kinetic, microperimetry, visual electrophysiology, mobility assessment and patient-related outcomes specifically National Eye Institute VQ-25 and others

The search strategy used was as follows: (Retinoschisis/ or x-linked juvenile retinoschisis.mp) and (visual acuity.mp

or OCT or electrophysiology.mp or microperimetry.mp or mobility.mo or wide field imagining.mp or fundus photography.mp or retinal photography.mp or autofluorescence or patient reported outcomes.mp or patient reported outcome measures/) all terms were expanded. We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28th February 2019. This study conforms to the tenets of Helsinki.

Study selection

We included randomized controlled trials (RCTs) evaluating efficacy or effectiveness of interventions for XLRS. Natural history studies of patients with XLRS included cohort studies where at least one group outcome measure, such as function (VA, electroretinogram) structure (OCT), and/or patient-related outcomes were being assessed longitudinally. The same test was required to be assessed on two different occasions.

Data collection and analysis

A data extraction form was developed by the reviewers, pilot tested on two studies and refined as required. Two reviewers (JRG and CYH) extracted data from the included studies and another reviewed verified the extracted data.

This systematic review evaluated studies that included retrospective reviews and randomized clinical trials. The randomized clinical trials were assessed for bias (all prospective studies) using the Cochrane Risk of Bias Tool for RCTs [26, 27]. Three authors assessed the risk of bias in the prospective studies. The risk of bias related to outcome measures was assessed using the Quality in Prognosis Studies (QUIPPS) tool [28]. Four authors independently assessed each study using the QUIPPS tool.

The Cochrane Risk of Bias Tool for RCTs evaluated random sequence generation, allocation of concealment, blinding of participants and personal, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The studies were classified as good quality, fair quality or poor quality (Supplementary Table 1).

The assessed risk of bias regarding outcome measures was evaluated using the QUIPPS tool assessing: sample selection, recruitment, completeness of follow-up, timing of diagnosis and blinding. In addition, whether there was evidence of selective outcome reporting or any other sources of bias. Disagreements between the review authors over the risk of bias in particular studies were resolved by discussion, with the involvement of a third review author where necessary. The studies were classified as high, moderate or low risk of bias (Supplementary Table 2).

Analysis and synthesis

A narrative synthesis with tabulated results was determined to be the best way to evaluate the identified studies which have a large heterogeneity in methodological quality, intervention and outcome measures [29]. It was not feasible to combine data by means of a meta-analysis. The systematic review has followed the PRISMA 2009 checklist to report systematic reviews [25] (Supplementary Table 3).

Specifically, we analyzed the data with respect to change in VA, change in visual electrophysiology parameters, change in OCT measurement of macular thickness.

Results

The results of the search and selection process are shown in Fig. 1. From a total of 2305 references initially identified, we selected 67 potentially relevant articles after title and abstract screening. Finally, 12 studies reported in 12 publications were included for review [20, 21, 30–39].

A significant limitation of all studies included in this systematic review is their clinic-based as opposed to population-based participants. In addition, only one study is a randomized clinical trial [20] and was classified as good quality. The risk of bias evaluation for the randomized clinical trials studies and outcome bias is presented in Supplementary Tables 1 and 2, respectively.

The main characteristics of the selected studies are presented in Table 1. The studies include four prospective series [20, 33, 36, 38] and eight retrospective case series, only one of these studies is a randomized clinical trial [20]. Five series are natural history observational studies [21, 30, 33, 36, 39] and seven are interventional series using
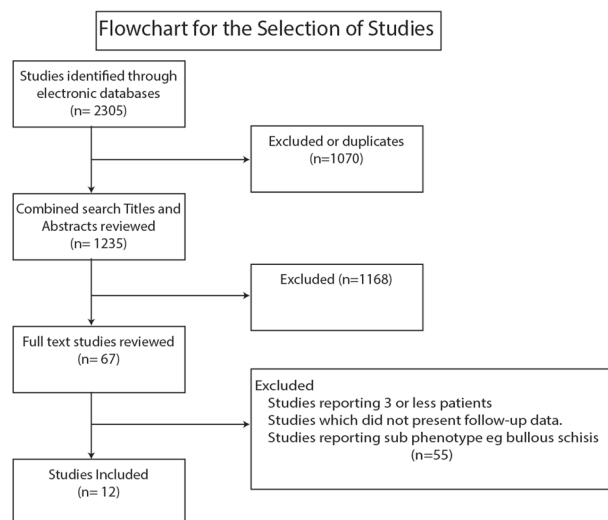

Fig. 1 Flowchart for the selection of studies.

Table 1 Details of X-linked retinoschisis studies meeting inclusion criteria.

Author	No. of cases	RS1 mutation identified (%)	Prospective/ retrospective	Natural history/ intervention	Primary outcome measures	Comments
Gurbaxani et al. [20]	11	7 (63.6%)	Prospective	Intervention	BCVA OCT	Acetazolamide
Apushkin et al. [38]	8	0 (0%)	Prospective	Intervention	BCVA OCT	Dorzolamide
Jeffrey et al. [33]	7	7 (100%)	Prospective	Natural history	BCVA FFERG micro-perimetry OCT	
Kjellstrom et al. [36]	10	3 (33%)	Prospective	Natural history	BCVA OCT FFERG mfERG Goldman VF	
Andreuzzi et al. [31]	36	17 (47.2%)	Retrospective	Intervention	BCVA OCT (qualitative)	Carbonic anhydrase inhibitors type (number of patients) Dorzolamide (31) Brinzolamide (3) Acetazolamide (1) Combination (1)
Verbakel et al. [32]	9	4 (44.4%)	Retrospective	Intervention	BCVA OCT	Acetazolamide all patients+ Brinzolamide 4 patients Dorzolamide 2 patients
Yang et al. [34]	4	0 (0%)	Retrospective	Intervention	BCVA OCT	Brinzolamide
Khandhadia et al. [35]	4	4 (100%)	Retrospective	Intervention	BCVA OCT	Dorzolamide
Genead et al. [37]	15	0	Retrospective	Intervention	BCVA OCT (time domain)	Dorzolamide
Cukras et al. [30]	120	120 (100%)	Retrospective	Natural history	BCVA FFERG OCT	80 with follow-up 55 FFERG with 29 follow-up FFERGs
Apushkin et al. [21]	38	0	Retrospective	Natural history	BCVA Goldman VF	31/38 patients' visual field
Roesch et al. [39]	92	91	Retrospective	Natural history	BCVA	

Note that the optical coherence tomography is spectral domain unless otherwise stated.

BCVA best corrected visual acuity, *OCT* optical coherence tomography, *FFERG* full-field electroretinogram, *mfERG* multifocal electroretinogram, *VF* visual field.

either topical carbonic anhydrase inhibitors [34, 35, 37, 38] or systemic carbonic anhydrase inhibitors or combination of topical and systemic agents [20, 31, 32]. No quality of life PROMs have been reported for XLRS.

Visual acuity outcomes

Typical approaches used to characterize VA include threshold events, e.g., a 15-letter loss or gain (doubling of the visual angle) or loss of VA to a level worse than 6/12 where the outcome compares the percentage of success or failure between different treatment groups [40]. Mean changes in best corrected VA (BCVA) have evolved to be the preferred primary outcome measure for clinical trials involving large subject numbers such as diabetic retinopathy or age-related macular degeneration, as this enables smaller sample sizes, increases precision and helps avoid issues of misclassification around a threshold of step changes on the scale [41].

The XLRS publications studies assessing VA outcomes were divided into two groups: those reporting natural history of XLRS and those reporting change in VA following an intervention (Table 2). All the intervention studies involved carbonic anhydrase inhibitors delivered topically or systemically. In the natural history observational group, two studies Kjellstrom et al. [36] and Apushkin et al. [21] showed no significant change in VA over the study period which had a mean follow-up of 10.2 years. Apushkin et al.

Table 2 Studies reporting visual acuity outcomes: natural history studies with comparison between time points.

Study	Outcome	Follow-up mean (range years)	Acuity test	Result	P value	Outcome significance definitions
Natural history observational studies						
Cukras et al. [30]	Annual rate of decline (letters/year)	6.67 (0.25–47)	ETDRS LogMAR	−0.22	0.65 OD and 0.22 OS eyes	$P < 0.05$
Jeffrey et al. [33]	Repeatability coefficient BCVA	0.75 (0)	ETDRS LogMAR	−0.01	0.94	±6 letters
Kjellstrom et al. [36]	Change in visual acuity between time points	12 (8–14)	Snellen acuity	No change described; data not presented	Not significant	$P < 0.05$
Apushkin et al. [21]	Change in visual acuity between time points	10.2 (1–28)	ETDRS LogMAR	OD Δ −0.002 OS Δ −0.016	Not significant	$P < 0.05$
Roesch et al. [39]	Change in visual acuity between time points	19.78 (1.5–31)	Snellen acuity	20/67–20/78 (Δ0.59 logMAR units)	Not measured 21.2% significant deterioration	≥doubling of visual angle
Intervention studies and change in visual acuity						
Andreuzzi et al. [31]	Change in acuity pre and post treatment		ETDRS LogMAR	−0.09	$P < 0.0001$	$P < 0.05$
Verbakel et al. [32]	Change in acuity pre and post treatment		ETDRS LogMAR	−0.14	$P < 0.05$	≥7 ETDRS letters
Gurbaxani et al. [20]	Change in acuity pre and post treatment		ETDRS LogMAR	−0.06	$P < 0.006$	$P < 0.05$
Yang et al. [34]	Change in acuity pre and post treatment		Snellen	0	Not significant	$P < 0.05$
Khandhadia et al. [35]	Change in acuity pre and post treatment		ETDRS LogMAR	−0.07	$P < 0.041$	$P < 0.05$
Genead et al. [37]	Change in visual acuity between time points		ETDRS LogMAR	−0.07	$P = 0.02$	≥7 ETDRS letters
Apushkin et al. [38]	Threshold number of patients meeting criteria		ETDRS LogMAR	5/8 (62.5%) Improved	Threshold 62.5% improved	≥7 ETDRS letters

BCVA best corrected visual acuity, *ETDRS* early treatment diabetic retinopathy study, *LogMAR* logarithm of the minimum angle of resolution, Δ change.

study presents data from which VA progression was calculated showing a decline of -0.01 LogMAR units per year, equivalent to loss of one letter every 2 years [21]. Roesch et al. reported a -0.00333 LogMAR unit decline per year equivalent to a 21.2% deterioration in VA over 19.8 years [39]. Jeffrey et al. reported that within-subject variability was relatively small compared with the differences in VA between subjects [33]. Cukras et al. reported an annual rate of VA decline of 0.22 letters per year as measured by ETDRS LogMAR chart [30]. The very slow decline in VA makes detecting change difficult. These studies suggest the VA loss is equivalent to 0.22–0.5 letters per year.

The second group reporting VA outcomes was for studies assessing the effects of topical or systemic carbonic anhydrase inhibitors (Table 2). Yang et al.'s was the only one of six studies in this group to report no improvement with carbonic anhydrase inhibitors [34]. The other five studies all reported significant improvement in VA.

Optical coherence tomography outcome measures

Assessment of change in OCT parameters has been affected by changing technology. Studies performed prior to 2008 used time domain OCT and could only measure gross outcomes such as qualitative assessment of cystic cavities and central macular thickness (CMT). Macular thickness in XLRS is not a matter of tissue thickness but a change in cavity dimension with age macular atrophy and cell loss develops. Eight studies were included that reported on outcomes using spectral domain OCT (SD-OCT) parameters (Table 3). Jeffrey et al. [33] examined the repeatability for SD-OCT measurements in patients over four visits and found that central retinal thickness (logOCT) did not change over the assessment period ($P = 0.81$). Seven studies reported on the change in macular thickness or appearance following the use of carbonic anhydrase inhibitors either topically or systemically. Only two studies were prospective, Apushkin et al. [38] and Gurbaxani et al. [20], with the latter being the only randomized study reported to date. A significant change in SD-OCT macular parameters was a change of >2 standard deviations from the pre-intervention mean measurement. Using these criteria four studies [32, 35, 37, 38] found significant reduction in SD-OCT parameters for CMT. Gurbaxani et al. [20] and Yang et al. [34] did not find a significant change in SD-OCT measured macular thickness following the use of carbonic anhydrase inhibitors. Andreuzzi et al. [31], the only observational study, qualitatively examined the SD-OCT appearance for resolution or change in cyst size and reported a 66% reduction in cyst size.

Bennet et al. proposed a more refined measure of retinal structure that designated the outer segment thickness

Table 3 Studies reporting optical coherence tomography and their outcome measures.

Study	Study and outcome	Measurement	Result	Significance	Outcome significance definitions
Gurbaxani et al. [20]	Prospective change in CMT pre and post intervention	CMT µm	Mean Δ 20.36 (6.4%)	$P = 0.3$	$P < 0.05$
Apushkin et al. [38]	Prospective observational change in FT and FZT	Number of patients meeting criteria	7/8 patients (87.5%)	Threshold	Δ FT > −19.6% Δ FZT > −17.1%
Jeffrey et al. [33]	Prospective observation repeatability coefficient CMT over 6 months	Significant change	31/18% (better/worse eye)	Not significant	
Andreuzzi et al. [31]	Retrospective change in cyst size pre and post intervention (categorical)	Appearance	66% cyst reduction	NA	
Verbakel et al. [32]	Retrospective percentage change in FZT pre and post intervention (threshold)	Percent change	55.6% of eyes had reduction	NA	Δ CMT > −22.4%
Yang et al. [34]	Retrospective change in CMT pre and post intervention	% change	3/4 patients	Threshold	Δ CMT > −19.6%
Khandhadia et al. [35]	Retrospective change in CMT pre and post intervention	CMT µm	Mean Δ 61 µm	$P = 0.007$	>2 SD reduction
Genead et al. [37]	Retrospective change in CFZ pre and post intervention	CMT µm	Mean Δ 95.5 µm	$P = 0.008$	Δ CFZ −17.1%

FT central foveal thickness, *FZT* foveal zone thickness within 1000 µm centred on foveola, *CFZ* central foveal zone central 1000 µm centred on the foveola, *CMT* central macular thickness, Δ change or increment, *SD* standard deviation, *NA* not applicable.

Table 4 Studies reporting visual electrophysiology and their outcome measures.

Study	Outcome measure	Measurement instrument	Result	Significance ($P < 0.05$)
Cukras et al. [30]	Change in 30-Hz latency (milliseconds per year)	30-Hz latency	0.123	$P = 0.02$
Jeffrey et al. [33]	Repeatability coefficient b/a ratio over 6 months	Change b/a ratio	0.44/0.23 (better/ worse eye)	Not significant
Kjellstrom et al. [36]	Change in FFERG parameters:			
	b-wave amplitude	Amplitude	No change	OD $P = 0.142$ OS $P = 0.573$
	30-Hz flicker amplitude	Amplitude		OD $P = 0.981$ OS $P = 0.683$
	30-Hz flicker latency	Amplitude and implicit time		OD $P = 0.904$ OS $P = 0.325$
	b/a ratio	Ratio size	1.2 ± 0.22 2nd 1.5 ± 0.65	Not significant

FFERG full-field electroretinogram.

defined as the distance between the ellipsoid zone and the retinal pigment epithelium [42]. They showed a strong correlation with BCVA [42]. Andreoli et al. postulated that the lack of correlation between CMT at the fovea and BCVA is due to the opposing effects of schisis and atrophy on thickness measurements [43]. Increased inner retinal thickness (retinal nerve fibre layer, ganglion cell layer, inner plexiform layer) from schisis and decreased perifoveal inner retinal thickness presumably from inner retinal atrophy have both been correlated with decreased VA [42].

Visual electrophysiology outcome measures

Two groups in three studies evaluated International Society for Clinical Electrophysiology of Vision standard electrophysiology outcomes (Table 4). XLRS characteristically produces an electronegative FFERG, whereby the photoreceptor-generated a-wave has the same or greater amplitude than the inner retina-generated b-wave. This is because the inner retina is the site of the pathology in XLRS. Hence, b-wave amplitude and the b/a ratio were natural choices in order to try and determine progression. The light adapted 30-Hz flicker test measures cone system sensitivity. The responses arise from on and off bipolar cells in the inner retina that connect to cone photoreceptors. Jeffrey et al. assessed variability of potential outcomes measures over a 6-month period. They found low variability in b-wave amplitude [33]. They commented that four of seven eyes in the worse eye group had b-waves that were similar to the background noise, which in turn, minimizes their contribution to the variability of the b/a ratio. They also found that the variability of light adapted 30-Hz flicker amplitude was small and similar to that of the FFERG a-wave. Cukras et al. and Jeffrey et al. reporting on cohorts from the same institution found that the 30-Hz latency did

change significantly over time suggesting that this may prove useful as another measure of safety [30, 33]. The study by Kjellstrom et al. was of significant duration in looking at change in ten patients over a mean of 12 years. This is noteworthy, compared with short-term studies. These authors found no significant change in b- wave amplitude, b/a ratio and 30-Hz flicker amplitude and latency [36].

Multifocal electroretinograms (mfERG) were evaluated by three groups [36, 44, 45]. The mfERG helps understand focal retinal function and depicts the distribution of the affected and unaffected retinal areas, which could be useful in future interventional therapeutic procedures, as well as in the follow-up of these patients. The pattern ERG was analyzed by Vincent et al. and found to be abnormal [46]. These macular electrophysiologic investigations were performed on one occasion preventing assessment of these investigations as markers of disease progression.

Correlation of functional and structural measures

In the treatment trials consideration has been given to whether the reduction in retinal cysts leads to improved VA. In five studies this was assessed [20, 31, 32, 35, 38]. It was only Apushkin et al. who showed a correlation between VA and OCT assessment of macular thickness in association with carbonic anhydrase inhibitor use [38]. In contrast, Gurbaxani et al. concluded that change in macular thickness may not always mean improvement in vision to the patient and this may be related to the pre-existing state of the retinal tissue [20]. Genead also found that there was only modest improvement (of 1 line not reaching significance) in VA even with appreciable improvement in cystic changes on OCT [37]. Apushkin et al. reported that those patients with non-cystic-appearing changes within the fovea, including

pigment mottling or an atrophic appearing lesion, tended to have a more appreciable degree of VA impairment compared with those patients with a cystic-appearing foveal change providing further evidence of an indirect association between macular thickness and VA [21].

Discussion

Summary of evidence

The outcome measures assessed included BCVA, OCT, CMT and visual electrophysiology. These outcome measures for monitoring XLRS were evaluated in 12 studies, including four prospective [20, 33, 36, 38] and eight retrospective case series. Five were natural history observational studies [21, 30, 33, 36, 39] and seven were interventional series using either topical carbonic anhydrase inhibitors [34, 35, 37, 38] or systemic carbonic anhydrase inhibitors or combination of topical and systemic agents [20, 31, 32]. Only one study was a prospective randomized study [20].

Visual acuity outcome measures

Measuring sensitivity to the change of a VA test is difficult, in that there is no independent gold-standard method of establishing whether true clinical change has occurred [47]. Detection of progression requires the separation of true change from measurement variability. For slowly progressive disease, true changes can be largely confounded by test–retest variability, when assessed over a relatively short period of time. While this can affect individual patient management, this variability may significantly affect endpoints and sample sizes used in clinical trials [48]. A change in 10–15 letters detected has been incorporated into study designs evaluating anti-vascular endothelial growth factor agents [47, 49, 50]. Two studies adopted a change of seven ETDRS letters as significant; using this criterion five of eight subjects reached this goal [32, 37].

VA has been shown through a number of natural history observational studies to remain relatively stable with only minimal deterioration [21, 30, 36]. The trials reported here show that stability occurs through 10–12 years of follow-up. One trial with mean follow-up of 19.7 years found a 21.2% decline in VA [39]. When VA was used as an outcome measure for intervention trials with topical or systemic carbonic anhydrase inhibitors (Table 2) five of the six studies reported statistically significant improvement in acuity according to their individual study protocols after treatment. One interventional observational study involving four children under 10 years of age did not find any significant improvement [34]. The relationship of statistically

improved VA and patient perception has not been evaluated by any study to date.

Optical coherence tomography outcome measures

OCT showed improvement in macular thickness parameters in four studies following carbonic anhydrase inhibitor therapy [32, 35, 37, 38], no significant reduction in macular thickness in two trials [20, 34] and in one study, the significance was not measured but qualitatively there was a reduction in macular schisis [31]. OCT macular measurements did not correlate with VA. Increasing age was associated with the macular becoming atrophic restricting the ability to correlate macular thickness improvement due to schitic thinning. Apushkin was the only publication reporting an association between VA and OCT parameters [38].

Electrodiagnostic outcome measures

The FFERG b/a ratio did not change from baseline and part of this may reflect a floor response. Whereas the light adapted 30-Hz flicker stimulus may correlate with disease status [37], which contrasts with Kjellstrom who found no change over time [36].

Cukras found a strong correlation for structural and functional measures between the two eyes highlighting the potential for monocular therapies to use the fellow eye as an appropriate comparison reference [30].

Patient-reported outcome measures

Patient-related outcomes are increasingly being identified as important in inherited retinal disorders [51]. To date they have not been reported for XLRS. These patients-reported functional levels offer an opportunity to further refine outcome measures.

Conclusion

This systematic review highlighted that VA was the measure most likely to show a statistically significant outcome. The reported change in VA although statistically significant was small raising the issue as to whether or not the change was functionally meaningful. The assessment of this VA change requires further evaluation to determine clinical usefulness. The rate of change of vision is slow in most cases; assuming no intervening peripheral schitic complication. Macular SD-OCT outcomes were variable with studies showing improvement in CMT but poor correlation with VA. OCT measurement of macular thickness includes all retinal layers. A more refined measure is that of outer segment thickness. This measurement should be

investigated longitudinally to assess the correlation with visual function. Visual electrophysiology provides an objective measure of retinal function and is readily tolerated by both children and adults. The limitation to wider use of visual electrophysiology in monitoring XLRS is the availability of testing centres appropriately equipped and staffed with trained technicians. The FFERG 30-Hz latency component was identified as a further functional parameter. PROMs provide a means to capture patient's perspectives on their health and impact of therapeutic interventions [52]. By providing validated and standardized patient assessed evidence of effectiveness they are becoming an important outcome measure. PROMs will be an area for future research to refine biomarkers used to evaluate natural history or novel therapies in XLRS.

Compliance with ethical standards

Conflict of interest JRG is a consultant to Novartis Pharmaceuticals Australia, no conflicting relationship exists for CYH, CLF, EEC, PJM or RVJ.

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References

1. Molday RS, Kellner U, Weber BHF. X-linked juvenile retinoschisis: clinical diagnosis, genetic analysis, and molecular mechanisms. Prog Retinal Eye Res. 2012;31:195–212.
2. Sauer CG, Gehrig A, Warneke-Wittstock R, Marquardt A, Ewing CC, Gibson A, et al. Positional cloning of the gene associated with X-linked juvenile retinoschisis. Nat Genet. 1997;17:164–70.
3. Forsius H, Krause U, Helve J, Vuopala V, Mustonen E, Vainio-Mattila B, et al. Visual acuity in 183 cases of X-chromosomal retinoschisis. Can J Ophthalmol. 1973;8:385–93.
4. Kim DY, Mukai S. X-linked juvenile retinoschisis (XLRS): a review of genotype-phenotype relationships. Semin Ophthalmol. 2013;28:392–6.
5. Riveiro-Alvarez R, Trujillo-Tiebas M-J, Gimenez-Pardo A, Garcia-Hoyos M, Lopez-Martinez M-A, Aguirre-Lamban J, et al. Correlation of genetic and clinical findings in Spanish patients with X-linked juvenile retinoschisis. Invest Ophthalmol Vis Sci. 2009;50:4342–50.
6. Pimenides D, George NDL, Yates JRW, Bradshaw K, Roberts SA, Moore AT, et al. X-linked retinoschisis: clinical phenotype and RS1 genotype in 86 UK patients. J Med Genet. 2005;42:e35.
7. Shinoda K, Ishida S, Oguchi Y, Mashima Y. Clinical characteristics of 14 japanese patients with X-linked juvenile retinoschisis associated with XLRS1 mutation. Ophthalmic Genet. 2000;21: 171–80.
8. Eksandh LC, Ponjavic V, Ayyagari R, Bingham EL, Hiriyanna KT, Andreasson S, et al. Phenotypic expression of juvenile X-linked retinoschisis in Swedish families with different mutations in the XLRS1 gene. Arch Ophthalmol. 2000;118:1098–104.
9. Xiao Y, Liu X, Tang L, Wang X, Coursey TG, Guo X, et al. X-linked retinoschisis: phenotypic variability in a chinese family. [Erratum appears in Sci Rep. 2016;6:21940 Note: Coursy, Terry [corrected to Coursey, Terry G]; PMID: 26960251]. Sci Rep. 2016;6:20118.
10. Xu F, Xiang H, Jiang R, Dong F, Sui R. Phenotypic expression of X-linked retinoschisis in Chinese families with mutations in the RS1 gene. Doc Ophthalmol. 2011;123:21–7.
11. Bowles K, Cukras C, Turriff A, Sergeev Y, Vitale S, Bush RA, et al. X-linked retinoschisis: RS1 mutation severity and age affect the ERG phenotype in a cohort of 68 affected male subjects. Invest Ophthalmol Vis Sci. 2011;52:9250–6.
12. Feinsod M. Safety and efficacy of rAAV-hRS1 in patients with X-linked retinoschisis (XLRS). ClinicalTrials.Gov. https://clinicaltrials.gov/ct2/show/NCT02416622?cond=Retinoschisis&draw=2&rank=2. Accessed 8 Apr 2018.
13. Clinical and genetic studies of X-linked juvenile retinoschisis. 2018. https://ClinicalTrials.gov/show/NCT02331173. Accessed 6 Jul 2018.
14. George N, Yates J, Bradshaw K, Moore A. Infantile presentation of X linked retinoschisis. Br J Ophthalmol. 1995;79:653–7.
15. Gerth C, Zawadzki RJ, Werner JS, Heon E. Retinal morphological changes of patients with X-linked retinoschisis evaluated by Fourier-domain optical coherence tomography. Arch Ophthalmol. 2008;126:807–11.
16. Bastos AL, Freitas BP, Villas Boas O, Ramiro AC. Use of topical dorzolamide for patients with X-linked juvenile retinoschisis: case report. Arq Bras Oftalmol. 2008;71:286–90.
17. Walia S, Fishman GA, Molday RS, Dyka FM, Kumar NM, Ehlinger MA, et al. Relation of response to treatment with dorzolamide in X-linked retinoschisis to the mechanism of functional loss in retinoschisin. Am J Ophthalmol. 2009;147:111.
18. Eksandh L, Andreasson S, Abrahamson M. Juvenile X-linked retinoschisis with normal scotopic b-wave in the electroretinogram at an early stage of the disease. Ophthalmic Genet. 2005;26: 111–7.
19. Fahim AT, Ali N, Blachley T, Michaelides M. Peripheral fundus findings in X-linked retinoschisis. Br J Ophthalmol. 2017;101: 1555–9.
20. Gurbaxani A, Wei M, Succar T, McCluskey PJ, Jamieson RV, Grigg JR. Acetazolamide in retinoschisis: a prospective study. Ophthalmology. 2014;121:802–3.
21. Apushkin MA, Fishman GA, Rajagopalan AS. Fundus findings and longitudinal study of visual acuity loss in patients with X-linked retinoschisis. Retina. 2005;25:612–8.
22. Wu Z, Saunders LJ, Zangwill LM, Daga FB, Crowston JG, Medeiros FA. Impact of normal aging and progression definitions on the specificity of detecting retinal nerve fiber layer thinning. Am J Ophthalmol. 2017;181:106–13.
23. Study of RS1 ocular gene transfer for X-linked retinoschisis. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02317887. Accessed 6 Jul 2018.
24. Mothers experiences with X-linked retinoschisis compared to fathers experiences. ClinicalTrials.gov. 2018. https://ClinicalTrials.gov/show/NCT03354403. Accessed 6 Jul 2018.
25. Moher D, Liberati A, Tetzlaff J, Altman DG,The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Med. 2009;6:e1000097.
26. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Joksimovic L, Koucheki R, Popovic M, Ahmed Y, Schlenker MB, Ahmed IIK. Risk of bias assessment of randomised controlled trials in high-impact ophthalmology journals and general medical journals: a systematic review. Br J Ophthalmol. 2017;101: 1309–14.

28. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158:280–6.

29. Ryan R. Cochrane Consumers and Communication Review Group: data synthesis and analysis. http://cccrg.cochrane.org. Accessed June 2013.

30. Cukras CA, Huryn LA, Jeffrey BP, Turriff A, Sieving PA. Analysis of anatomic and functional measures in X-linked retinoschisis. Invest Ophthalmol Vis Sci. 2018;59:2841–7.

31. Andreuzzi P, Fishman GA, Anderson RJ. Use of a carbonic anhydrase inhibitor in X-linked retinoschisis: effect on cystic-appearing macular lesions and visual acuity. Retina. 2017;37:1555–61.

32. Verbakel SK, van de Ven JP, Le Blanc LM, Groenewoud JM, de Jong EK, Klevering BJ, et al. Carbonic anhydrase inhibitors for the treatment of cystic macular lesions in children with X-linked juvenile retinoschisis. Invest Ophthalmol Vis Sci. 2016;57:5143–7.

33. Jeffrey BG, Cukras CA, Vitale S, Turriff A, Bowles K, Sieving PA. Test-retest intervisit variability of functional and structural parameters in X-linked retinoschisis. Transl Vis Sci Technol. 2014;3:5.

34. Yang FP, Willyasti K, Leo SW. Topical brinzolamide for foveal schisis in juvenile retinoschisis. J Aapos. 2013;17:225–7.

35. Khandhadia S, Trump D, Menon G, Lotery AJ. X-linked retinoschisis maculopathy treated with topical dorzolamide, and relationship to genotype. Eye. 2011;25:922–8.

36. Kjellstrom S, Vijayasarathy C, Ponjavic V, Sieving PA, Andreasson S. Long-term 12 year follow-up of X-linked congenital retinoschisis. Ophthalmic Genet. 2010;31:114–25.

37. Genead MA, Fishman GA, Walia S. Efficacy of sustained topical dorzolamide therapy for cystic macular lesions in patients with X-linked retinoschisis. Arch Ophthalmol. 2010;128:190–7.

38. Apushkin MA, Fishman GA. Use of dorzolamide for patients with X-linked retinoschisis. Retina. 2006;26:741–5.

39. Roesch MT, Ewing CC, Gibson AE, Weber BH. The natural history of X-linked retinoschisis. Can J Ophthalmol. 1998;33:149–58.

40. Csaky K, Ferris F, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. Invest Ophthalmol Vis Sci. 2018;58:3456–63.

41. Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology. 2007;114:1804–9.

42. Bennett LD, Wang YZ, Klein M, Pennesi ME, Jayasundera T, Birch DG. Structure/psychophysical relationships in X-linked retinoschisis. Invest Ophthalmol Vis Sci. 2016;57:332–7.

43. Andreoli MT, Lim JI. Optical coherence tomography retinal thickness and volume measurements in X-linked retinoschisis. Am J Ophthalmol. 2014;158:567–73.

44. Sen P, Roy R, Maru S, Ravi P. Evaluation of focal retinal function using multifocal electroretinography in patients with X-linked retinoschisis. Can J Ophthalmol. 2010;45:509–13.

45. Huang S, Wu D, Jiang F, Luo G, Liang J, Wen F, et al. The multifocal electroretinogram in X-linked juvenile retinoschisis. Doc Ophthalmol. 2003;106:251–5.

46. Vincent A, Robson AG, Neveu MM, Wright GA, Moore AT, Webster AR, et al. A phenotype-genotype correlation study of X-linked retinoschisis. Ophthalmology. 2013;120:1454–64.

47. Rosser DA, Cousens SN, Murdoch IE, Fitzke FW, Laidlaw DA. How sensitive to clinical change are ETDRS logMAR visual acuity measurements? Invest Ophthalmol Vis Sci. 2003;44:3278–81.

48. Wu Z, Medeiros FA. Impact of different visual field testing paradigms on sample size requirements for glaucoma. Clin Trials Sci. 2018;8:4889.

49. Wolf S, Balciuniene VJ, Laganovska G, Menchini U, Ohno-Matsui K, Sharma T, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology. 2014;121:682.

50. Canadian Agency for Drugs and Technologies in Health. Ranibizumab (Lucentis): visual impairment due to choroidal neovascularization secondary to pathologic myopia. 2015. https://www.ncbi.nlm.nih.gov/books/NBK349551/.

51. Chaumet-Riffaud AE, Chaumet-Riffaud P, Cariou A, Devisme C, Audo I, Sahel JA, et al. Impact of retinitis pigmentosa on quality of life, mental health, and employment among young adults. Am J Ophthalmol. 2017;177:169–74.

52. Tadic V, Rahi JS. One size doesn't fit all: time to revisit patient-reported outcome measures (PROMs) in paediatric ophthalmology? Eye. 2017;31:511–8.