

Uveitis

# How do you know?

J T Rosenbaum, A Deodhar, E B Suhler, J R Smith

## Some thoughts on judging efficacy in treating patients with uveitis

How do you know if your patient improves with any particular therapy? In the treatment of patients with vision threatening uveitis, the primary goal of therapy is far from universally accepted. Should the end point be improvement in visual acuity? An obvious choice but flawed since many patients benefit without a discernable change in acuity measurements. Cataract and macular scars can limit the improvement in acuity even as inflammation is controlled. In addition, acuity measurements do not reflect lighting, effort, or the sporadic variability that some patients observe with uveitis. Should the goal be reduced inflammation as judged by examination? How about improved visual function as judged by patient questionnaire or by physician assessment? Can a drug be deemed efficacious if it results solely in the reduction in a potentially toxic medication such as corticosteroid? Is stabilisation of acuity an adequate goal? If judging benefit is so complex, is there a way to use a single instrument to accommodate multiple potential end points? As we enter an era of trying to base medical decision making on evidence, we need to decide what evidence to accept.

Rheumatologists have long faced a similar dilemma in judging the efficacy of treatments for autoimmune diseases such as rheumatoid arthritis and

systemic lupus erythematosus. The solution has been to rely on expert panels that have tested composite scores which combine objective measures of disease activity with functional outcomes. These disease indices include the ACR20, ACR50, ACR70, ACR-N, ACR-AUC, and DAS.<sup>1,2</sup> For example, the ACR20 is defined as 20% improvement in tender and swollen joint scores plus 20% improvement in three out of the following five parameters: patient's global assessment, physician's global assessment, level of pain on a visual analogue scale, health assessment questionnaire measuring function, and sedimentation rate.<sup>1</sup> This instrument has been widely employed in judging benefit in clinical trials for rheumatoid arthritis.

The randomised controlled trial (RCT) is generally considered the gold standard for assessing clinical efficacy. RCTs are frequent in some medical fields such as oncology and they are increasingly common in the treatment of rheumatological diseases. RCTs in ophthalmology such as the ONTT,<sup>3</sup> COMS,<sup>4</sup> OHTS,<sup>5</sup> and the ETDRS<sup>6</sup> have provided insights that now guide many therapeutic decisions. RCTs have only rarely been undertaken for ocular inflammatory disease, in part because of the relative rarity of these diseases. But RCTs for uveitis are also challenging because judging efficacy is not a straightforward task. Thus, some trials begin with inflammation that is quiescent and ascribe efficacy if other systemic immunosuppressive therapy is reduced.<sup>7</sup> Other trials judge efficacy based on the more conventional improvement in visual acuity. A measure of efficacy that could accommodate patients with active disease who are failing conventional therapy, patients with controlled disease who are receiving potentially toxic therapy, and patients whose visual function improves even without a measurable change in visual acuity would be a major boon to encouraging clinical trials.

**Both patients and physicians would benefit on agreement as to what constitutes clinical improvement**

There is a need for the development of a standardised approach in choosing

outcome measures in clinical trials of therapies in uveitis by the international ophthalmology community. End points or outcome measures may quantify: objective physical signs such as cell counts on slit lamp examination, vitreous haze, or visual acuity; macular oedema as measured by ocular coherence tomography or fluorescein angiography; reduction in a potentially toxic medication; and visual functional status as perceived by the patient and the physician. Each individual outcome measure will need to be "weighted" for importance according to the evidence from previous trials, their validity (see table 1), reliability, and their discriminatory power to assess "change over time."<sup>8,9</sup> Each outcome measure should contribute significant and non-duplicated information. Once a "core set" of such outcome measures is prepared from the recommendations from the experts in the field, consensus could be reached by discussions to develop a composite outcome measure that incorporates separate individual end points. Future clinical trials could then test the robustness of this new instrument.

Biological therapies that alter immune mediated diseases are emerging for difficult therapeutic challenges including rheumatoid arthritis,<sup>10</sup> Crohn's disease,<sup>11</sup> systemic lupus erythematosus,<sup>12</sup> psoriasis,<sup>13</sup> spondyloarthritis,<sup>14</sup> and transplant rejection.<sup>15</sup> It is extremely likely that some of these therapies will find a niche in the treatment of patients with uveitis. Indeed, some uncontrolled trials for several of the biological therapies are very encouraging,<sup>7,16</sup> while some small RCTs have been less enthusiastic for other biological treatments.<sup>17</sup>

We believe that the testing of biological and other novel therapies for uveitis needs to be encouraged, that this testing can be facilitated by utilising a composite index which recognises that improvement can be reflected in different fashions, and that such an index is best validated by a panel of experts using consensus to assess benefit similar to what has been achieved in rheumatology based on testing of the index on illustrative cases.

Currently, we are not able to answer the question, "How do you know?" While a hug from a grateful patient is gratifying, hugs are difficult to measure in RCTs. Both patients and physicians would benefit on agreement as to what constitutes clinical improvement. As our treatment decisions become evidence based, we need to look critically at what evidence should be employed.

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**Table 1** Validity parameters for outcome measures

Construct validity	Disease activity measures should change in the same direction as the patient changes clinically
Content validity	All aspects of clinical change should be captured by a set of outcome measures (not necessarily by each one)
Face validity	Outcome measures should appear sensible
Criterion validity	Ability of outcome measure to predict a long term outcome of importance
Discriminant validity	Outcome measure's responsiveness or sensitivity to change

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## ECHO.....

### Genetic analysis points to apoptotic mutation in glaucoma



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A major cause of blindness may, after all, stem from changes in gene p53, contrary to other data, according to a study showing a link with p53 haplotypes in a Caucasian population. This is further evidence to support programmed cell death in causing primary open angle glaucoma (POAG).

The distribution of haplotypes with two polymorphic variants—a 16 base pair insertion in intron 3 and C to G base pair (proline to arginine) change at codon 72 in exon 4—within the p53 gene was significantly different between patients with POAG and controls. Of the four possible haplotypes, only subjects with the insertion-arginine haplotype were significantly more likely to have glaucoma—12.5% versus 0.68% for controls.

The study compared frequency distribution of p53 haplotypes between 140 unrelated patients with POAG and 73 unrelated healthy age and sex matched controls with clear differences in cardinal measures of POAG between them. Haplotypes were identified by p53 gene amplification and RFLP analysis.

Other studies have not shown an association between p53 variants and disease. The authors of this study interpret this as a result of methodological differences and to the notion that neither variant is the key variant, but that this is in linkage disequilibrium with the insertion-arginine haplotype.

POAG affects 70 million people world wide. Research has indicated that multiple genes may play a part, and the discovery that apoptosis of retinal ganglion cells is an important cause of glaucoma has raised the possibility that both may determine susceptibility.

▲ Ressiniotis T, *et al*. *Journal of Medical Genetics* 2004;**41**:296-298.



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