How should diagnostic tests be evaluated in glaucoma

How should diagnostic tests be evaluated in glaucoma?

Felipe A Medeiros

Clinicians are faced each day with the challenge of deciding appropriate management for patients suspected of having glaucoma. This decision is, at least in part, based on the results of diagnostic tests. The continuing proliferation of medical technology and introduction of new diagnostic tests renders the clinician's ability to critically evaluate these tests more important than ever. In the study by Reus and colleagues,¹ published in this edition of the Journal, they evaluated the diagnostic accuracy of two imaging technologies – GDx VCC and HRT I – and compared that with subjective assessment of stereoscopic photographs of the optic nerve head. These three methods were evaluated in their ability to discriminate subjects who had glaucomatous visual field loss and corresponding optic nerve head changes from healthy individuals with normal visual fields and normal optic nerves. Their comparison provides further insight into the ability of these technologies to detect known glaucomatous damage and provides an important comparison with subjective methods that have long been in use such as stereophotograph evaluation.

Most diagnostic studies in glaucoma have employed a case-control design similar to the one used in the work by Reus *et al.*¹ including glaucoma patients (cases), defined based on the presence of repeatable characteristic glaucomatous visual field defects; and normal subjects (controls), generally required to have normal visual fields, normal intraocular pressures and healthy appearance of the optic nerve. These studies are clearly important to provide an initial exploratory evaluation of the ability of these tests to detect glaucomatous damage. That is, if a test fails to differentiate cases from controls at this stage, no more evaluation would be pursued and the test would be generally regarded as not clinically useful. If the test succeeds in discriminating between these two groups, then further steps should be taken to evaluate whether it is able to provide clinically relevant information.

The starting point of any diagnostic process is the patient presenting with a constellation of symptoms and signs and

the clinician integrating this information to assign a level of certainty regarding the presence of disease. In the case of glaucoma evaluation, the process generally starts with the medical interview and history taking, followed by clinical examination, which generally includes slit-lamp examination, intraocular pressure measurement and optic nerve examination. For example, consider a 53 year-old white male with intraocular pressure of 25 mmHg, no family history of glaucoma, normal slit-lamp examination and suspicious neuroretinal rim thinning. After this information is collected, the clinician hypothesizes about the chance that glaucoma is present and can order additional tests, such as a visual field test. If the visual field results are normal or inconclusive, the clinician can order additional tests to try to minimize the margin of error regarding the uncertainty of diagnosis, such as an evaluation of the optic nerve head and/or retinal nerve fibre layer by imaging instruments. However, estimates of diagnostic accuracy of imaging instruments obtained from case control studies that include only patients with visual field loss and healthy subjects will not be directly applicable to the evaluation of patients suspected of having glaucoma such as the one described above, as this patient clearly does not fall into either one of these two categories. Therefore, when evaluating diagnostic studies, it is important to appraise whether the test has been evaluated on a population that is representative of the one in which the test is going to be applied in clinical practice.

To better understand some of the limitations of diagnostic studies in glaucoma, it is useful to trace parallels on how diagnostic studies are conducted in other areas of clinical medicine, such as cardiology, for example. How are studies evaluating a diagnostic test for myocardial infarction performed? In a recent review, Panju *et al.*² evaluated the accuracy of several diagnostic tests for myocardial infarction (MI). Eight studies evaluating the diagnostic accuracy of electrocardiogram (ECG) for detecting MI were selected. In all these studies, included patients were required to be suspected of having MI at the time of

ECG evaluation. These patients presented with chest pain to the emergency room and underwent an ECG evaluation for diagnostic purpose. Subsequently, they were divided into two groups, cases and controls according to a reference standard for diagnosis of MI, which was the level of cardiac enzymes in all studies. Cases were the ones with increased levels of cardiac enzymes and confirmed MI, whereas controls were the ones with normal enzyme levels who ended up having other causes for their chest pain, such as dyspepsia. The accuracy of ECG was then compared to the reference standard for detection of MI. Estimates of diagnostic accuracy for ECG obtained from these studies are likely to be valid in the common clinical situation of a patient presenting with chest pain and suspected of MI. The important point here being the fact that all patients were suspected of having the disease at the beginning of the study, that is, there was diagnostic uncertainty. In fact, the presence of diagnostic uncertainty is considered a fundamental requirement for a clinically relevant study evaluating a diagnostic test.^{3–5} According to the American Medical Association evidence-based guidelines for evaluation of the medical literature, one of the fundamental questions to be asked during evaluation of the validity of a diagnostic study is “Did clinicians face diagnostic uncertainty?”.³ In studies with no diagnostic uncertainty, the power of the test to detect disease tends to be overestimated. Lijmer *et al.*⁴ evaluated the impact of design-related bias in studies of diagnostic tests. They found that studies with a case-control design including patients with well-established disease and a separate group of normal control subjects resulted in a 3-fold overestimation of the power of the test.

The evaluation of diagnostic tests in patients suspected of having glaucoma has, however, a major limitation – the inexistence of a perfect reference standard for the disease. Unfortunately, at least until now, glaucoma cannot be diagnosed by simple blood tests and it is difficult, if not impossible, to ascertain the true diagnosis in a patient suspected of having glaucoma based on a single evaluation in time. Longitudinal follow-up is generally required to evaluate the existence of progressive damage which would then confirm the diagnosis. The final diagnosis based on longitudinal follow-up could then be used as a reference standard to which the results of the imaging instruments would be compared.⁶

In addition, it is also important to keep in mind possible relationships between the reference standard and the tests being evaluated and how they could affect the estimates of diagnostic accuracy. If one of

the tests in more correlated to the reference standard than the others, it will most likely perform better than the other tests. For example, if the reference standard included optic nerve head assessment at the slit lamp and one of the tests being evaluated involves the assessment of optic nerve head stereophotographs, its performance will likely be overestimated, as the appearance of the optic nerve head in photographs will be highly correlated to that at the slit lamp. This does not necessarily invalidate the study, but clinicians have to be aware of these issues so that they can evaluate the applicability

of diagnostic accuracy estimates in the relevant population.

Br J Ophthalmol 2007;**91**:273–274.
doi: 10.1136/bjo.2006.107409

Correspondence to: Felipe A Medeiros, M.D., Ph.D., Hamilton Glaucoma Center, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093–0946; fmedeiros@eyecenter.ucsd.edu

REFERENCES

- 1 Reus NJ, de Graaf M, Lemij HG. Accuracy of GDx VCC, HRT I, and clinical assessment of stereoscopic optic nerve head photographs for

diagnosing glaucoma. *Br J Ophthalmol* 2007;**91**:313–8.

- 2 Panju AA, Hemmelgarn BR, Guyatt GH, *et al*. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998;**280**:1256–63.
- 3 Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *Jama* 1994;**271**:389–91.
- 4 Lijmer JG, Mol BW, Heisterkamp S, *et al*. Empirical evidence of design-related bias in studies of diagnostic tests. *Jama* 1999;**282**:1061–6.
- 5 van der Schouw YT, Verbeek AL, Ruijs SH. Guidelines for the assessment of new diagnostic tests. *Invest Radiol* 1995;**30**:334–40.
- 6 Medeiros FA, Zangwill LM, Bowd C, *et al*. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am J Ophthalmol* 2005;**139**:1010–8.

Treatment of uveitis

Adalimumab in the therapy of uveitis in childhood

Ahmad M Mansour

"Adalimumab is more effective" ...?

Worldwide, around one million patients have been treated with tumour necrosis factor (TNF)- α antagonists (etanercept, infliximab or adalimumab) for rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease. Treatment results in substantial improvement in the signs and symptoms of arthritis (inhibition of progression of radiographic joint damage in psoriatic arthritis, resumption of growth in juvenile idiopathic arthritis (JIA) and attenuation of spinal inflammation in ankylosing spondylitis) as well as improved functional status and quality of life.¹ The use of TNF antagonists in adult uveitis has also been promising in small series.^{2–4} Recently, TNF antagonists were also used in paediatric uveitis^{5–6} and studies have shown the superiority of infliximab to etanercept in juvenile uveitis.⁷ Vasquez-Kobian *et al*⁸ released their results in October 2006 regarding the use of adalimumab in juvenile uveitis. Similarly in this issue, Biester *et al*⁹ report that the use of adalimumab in refractory juvenile uveitis has good visual outcome (see pages 319). However, since the approval of TNF antagonists, concerns have been raised regarding their safety especially in children. We describe the differences between the three biologic therapies regarding modes of action, visual results, side effects and economic impact on health, and review preliminary

evidence suggesting the potential superiority of adalimumab in JIA uveitis.

Adalimumab is a fully human immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to TNF and neutralises the biological activities of this cytokine by blocking its interaction with the p55 and p75 cell surface TNF receptors. Given the known role of TNF in uveitis, the efficacy and safety of adalimumab in the treatment of uveitis in JIA was analysed by Biester *et al*.⁸ Chronic asymptomatic anterior uveitis occurs in 10–30% of patients with JIA, usually within 4 years of the onset of arthritis, and is associated with a high frequency of non-specific low-titre antinuclear antibodies. Long-term visual outcome in JIA-associated uveitis has been described as poor, with one third of patients developing substantial visual impairment and 10% becoming blind.^{6–9} Most patients with JIA are already on non-steroidal anti-inflammatory drugs because of their arthritis and the drug of choice for polyarthritis is frequently methotrexate. According to several recent reports, low-dose oral methotrexate is effective in the treatment of chronic non-infective uveitis.⁹ However, if more effective treatment is needed, systemic glucocorticosteroids and/or low-dose cyclosporine are added. In patients with refractory chronic uveitis, treatment with a TNF antagonist is indicated.⁶

The three TNF antagonists (etanercept, infliximab and adalimumab) had similar efficacy in rheumatoid arthritis, but that

does not appear to be the case with uveitis, where infliximab is more effective than etanercept in both childhood⁷ and adult uveitis.^{4–10} Both adalimumab and infliximab were effective in reducing uveitis flares in patients with spondylarthropathy but etanercept was not.¹¹ Although infliximab was an effective short-term immunosuppressive agent with clear benefit, the rate of serious toxic effects was unexpectedly high in a prospective study.² Adalimumab was effective in controlling 80.8% of paediatric uveitis cases,⁵ three cases of Behcet uveitis resistant to infliximab³ and spondyloarthropathy-related uveitis.¹¹ Ocular response to adalimumab in JIA uveitis occurred within the first 2–6 weeks of therapy.⁵ Arthritis response to adalimumab was much faster with 10 (22.2%) of 45 patients achieving a clinical response within 24 h of dosing.¹² In this issue, Biester *et al*⁸ found retrospectively that adalimumab was well tolerated and decreased the relapse rate in JIA uveitis cases previously unresponsive to combined therapies (including infliximab), with minimal side effects (absence of anaphylactic reaction or infection).

To explain the therapeutic discrepancy between TNF- α antagonists, several hypotheses have been put forward relating to differences in molecular structure, mechanism of action, pharmacokinetics (kinetics, route and frequency of administration, type of TNF binding) and pharmacodynamics (apoptosis induction, TNF immunoprecipitation) (table 1).^{1–13} Etanercept and infliximab have different binding characteristics, with infliximab and adalimumab binding to both soluble and membrane-bound TNF, while etanercept binds primarily to soluble TNF. These differences in binding may manifest as differing effects on complement activation and apoptosis. Etanercept and infliximab also have different pharmacokinetic profiles that may influence their activity. Because infliximab is administered as