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EDITORIAL

Verteporfin photodynamic therapy in the UK: implications of the NICE appraisal

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Photodynamic therapy with verteporfin (otherwise known as verteporfin therapy) has been licensed in more than 65 countries, including the UK, for use in patients with predominantly classic subfoveal choroidal neovascularisation (CNV) as a result of age-related macular degeneration (AMD). However, a patchy and slow introduction in the UK has led to confusion, frustration, and some distress among patients, ophthalmologists, and professional representative bodies. Similar scenarios have arisen with new interventions in other UK medical specialities, but verteporfin therapy is the first high-profile case in ophthalmology. The handling of the introduction of this new therapy has far-reaching and worrying implications.

Evidence for the efficacy of verteporfin therapy comes from the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) Investigation,[1,2] which studied 609 patients with subfoveal CNV with a classic component caused by AMD (lesions with greatest linear dimension $\leq 5400\,\mu$m, best-corrected visual acuity 6/21–6/60). After 12 and 24 months of follow-up, the verteporfin group had a reduced risk of moderate and severe vision loss compared with the placebo group. A greater benefit was seen in the planned subgroup of patients with predominantly classic lesions (classic CNV makes up $\geq 50\%$ of the area of the entire lesion) at the baseline: after 24 months, 94 (59%) of 159 verteporfin-treated patients compared with 26 (31%) of 83 placebo-treated patients maintained or improved vision (<15 letters lost on a 1 m logMAR chart) ($P<0.001$). Recent results from the Verteporfin In Photodynamic therapy (VIP) Trial also showed verteporfin therapy provides a significant treatment benefit in selected patients with presumed recent disease progression and a lesion composed of occult subfoveal CNV with no classic because of AMD.[3]

The evidence from the TAP Investigation and VIP Trial is persuasive; however, some study limitations have been noted. Reliance on data from a single study (VIP Trial for occult with no classic CNV) and from a subgroup analysis (TAP Investigation for predominantly classic CNV) has been criticised by a number of independent groups including the Cochrane Eyes and Vision Group.[4] Further placebo-controlled studies have been called for including studies of extended visual functioning and quality of life, although these may prove difficult to fund. Study data from TAP and VIP have gained wide acceptance—they have been incorporated by the American Academy of Opthalmology in its Preferred Practice guidance and accepted by regulatory authorities for the European Union, Canada, and Australia. In the UK, in an informal survey of past delegates to the Medical Retina Group, only 17% of respondents indicated that in their opinion the use of verteporfin therapy should be restricted to use within a clinical trial, whereas 97% indicated that they believed that the evidence from TAP is sufficient to justify the use of verteporfin therapy in patients with predominantly classic CNV.[5]

After a European Union licence was granted in July 2000, a small number of specialist centres in the UK began providing care through the National Health Service (NHS) on a named patient basis. Also in 2000, the Safety and Efficacy Register of New Interventions and Procedures (SERNIP) gave a 'B' classification grade to the treatment for classic CNV with verteporfin therapy—'efficacy established, further evaluation required to confirm safety: procedure can be used as part of a surveillance programme registered with SERNIP'. As a

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result, a national surveillance programme was established under the auspices of the Medical Retina Group, and began data collection in mid-2001. The Royal College of Ophthalmologists established a working party, which in its second guidance notice in February 2001, recommended formal commissioning of verteporfin therapy for selected groups of patients with classic or predominantly classic subfoveal CNV and the introduction of named patient treatment programmes as an interim measure. At around the same time, the Department of Health referred the intervention to the National Institute for Clinical Excellence (NICE) to conduct an appraisal of verteporfin therapy for the treatment of CNV due to AMD to provide 'clear authoritative guidance' to the NHS.

Since this initial flurry of activity, and in the absence of guidelines, providers have had to develop policies as best as they can. These vary considerably, from open access service contracts, with different criteria and activities, to complete denial of access. Many healthcare purchasers will consider specific cases on a named patient basis, others will not. This national variation in policy has produced a sharp increase in administration for provider trusts and ophthalmology services and has resulted in difficult and delicate discussions with patients about 'postcode access'. Matters have been made worse by the reorganisation of providers and the introduction of Primary Care Trusts (PCTs), which are lacking in identified leads. Inadequate access to verteporfin therapy means that elderly patients may have to make long and frequent journeys to the few established centres—some are not able to make the necessary journey at all.

In August 2001, NICE issued a scope document and formed an Appraisal Committee to construct guidance on verteporfin therapy for the NHS. Invited consultees included the Royal College of Ophthalmologists, patient and carer groups, experts, and the sponsor (Novartis Ophthalmics). An Appraisal Consultation Document (ACD) was produced in April 2002, followed by a Final Appraisal Determination (FAD) 1 month later.[6]

The FAD recommended that verteporfin therapy should be restricted to patients with predominantly classic subfoveal CNV in the better-seeing eye (or only functioning eye) if the VA is 6/36 or better. It further recommended that verteporfin therapy 'should be carried out only in centres specialising in this treatment and as part of an ongoing nationally co-ordinated collection of robust and relevant data on clinical outcome and cost-effectiveness, including quality of life…'. Following publication of the FAD, appeals were lodged by all consultees. At the same time, the Department of Health indicated that central funding would not be made available for the proposed national surveillance programme. As a result, the FAD was withdrawn and a further appraisal round launched.

A second ACD was issued on 14th October 2002 with a third set of recommendations comprising restriction to entirely classic lesions.[7] The restriction to second eyes and visual acuity of 6/36 was removed, while the recommendation of centres specialising in the treatment and a national surveillance programme was retained. Consultees have once again submitted evidence but the earliest date before a second FAD can be issued is January 2003.

At each of the three stages of the appraisal process, a different set of recommendations has been made in spite of the available evidence remaining largely the same and the recommendations by the RCOphth being consistent throughout. It is therefore extremely difficult to predict the next set of recommendations but it is possible to consider the potential impact of each of the components that have been recommended to date in various combinations. Each of them has major implications for ophthalmological practice in the UK.

The most important issue is that of restricting treatment to the only, or better-seeing, eye. Should this precedent be established, clinical practice will become extremely difficult, not just for AMD but for other areas such as vitreoretinal surgery and cataract. In the case of AMD, it is not possible to judge which the better-seeing eye will be, for instance, over a 10-year period. The Macular Photocoagulation Study (MPS) clinical trials showed that, of 670 fellow eyes with no CNV at baseline, CNV developed in 236 (35%) within 5 years.[8] Justifying the likely loss of vision in the first eye to patients in our clinics will be uncomfortable and there will be a tendency to drive first eye treatments into the private sector. Although the economic rationlisation made by the Appraisal Committee may stand up to pure financial logic it is unlikely to be acceptable to the general public and, therefore, politically, especially if applied to all sight-threatening eye diseases.

The second main area of concern is the choice of 6/36 as the lower limit of visual acuity for eyes to receive treatment. This guidance is surprising because the clinical trial data from TAP showed a beneficial effect in patients with visual acuity between 6/21 and 6/60. Indeed, there was an even distribution of the baseline visual acuity between patients with visual acuity 6/12–6/24 (50.5%) and 6/30–6/60 (49.5%).[1] This is supported by data from the national surveillance programme,[9] which measured response rate (the loss of fewer than 15 logMAR letters) in patients with predominantly classic CNV at 12 months. Of those patients who were followed up for 12 months, response rates were similar irrespective of baseline visual acuity. Fewer than 15 letters of visual acuity were lost by 71% of patients with

baseline visual acuity of at least 45 letters (6/36) of 68% of patients with visual acuity 35–44 letters (6/60). This was slightly better than the proportion of responders in the predominantly classic subgroup of the TAP Investigation.

A restriction to lesions comprising entirely classic CNV will limit therapy to a very small minority of patients. The term applies to a group of patients that has not been studied separately in clinical trials to date and excludes any patient with a lesion containing elevated blocked fluorescence, thick blood occult CNV, or serous pigment epithelial detachment. It is possible that the appraisal team have mistaken this term for classic/no occult as used in TAP in which case the restriction will not be so tight. However, a significant though as yet unquantifiable group of patients with a lesion containing any occult component will still be excluded.

Some issues in the proposed national surveillance programme need to be addressed including the support costs and the data to be collected. The collection of quality of life data has not yet been shown to provide information beyond what is obtained by best-corrected visual acuity, and cost-effectiveness cannot be computed from current clinical trial data until adequate utility values are obtained in patients. The only utility data available to date are from physician interview in the US in approximately 100 patients.[10] The economic considerations of introducing verteporfin therapy are important, and robust cost-effectiveness data are clearly needed. However, these are not available at present—the economic analysis used by the NICE appraisal group was based on the whole TAP population rather than the subgroup of patients with predominantly classic CNV for whom the therapy is licensed.

UK ophthalmologists, particularly those specialising in medical retina, have had to come to terms with a set of circumstances that has applied only rarely in the past but is more likely in the future. An effective new intervention has been largely withheld during a lengthy and tortuous review process. Ophthalmologists need to engage to a much greater extent directly in the process of introducing a new technology and learn the key steps to successful expansion. A close relationship with trust and directorate teams is essential to present a united approach to purchasers. At all stages, the decision not to treat must be clearly identified as resting with purchasers rather than the clinician faced with counselling their patient. In the absence of guidance from NICE, local arrangements are advocated for the managed introduction of new technologies for any intervention, and colleagues should be prepared to cite HSC 1999/176 to argue for treatment of individual patients 'under exceptional circumstances'.[11] Purchasers, who have a duty to consider patients on an individual basis, cannot use the NICE referral process to deny treatment and are not permitted to issue blanket policies on any intervention.[12] Consultants need to ensure that sufficient support (revenue and capital) is provided for expensive service developments and take an active role in establishing costs. If verteporfin therapy is funded at the cost of the drug only, it will result in major pressures within any department and a big missed opportunity for funded service development. As a speciality, ophthalmology should look at any new service development as a chance to gain new resources and expand overall care provision for our patients.

In the absence of acceptable treatment recommendations from NICE, the highly unsatisfactory situation of unequal access persists. If, as is likely a further round of consultation and appeals takes place after the publication of the next FAD, the process will probably extend well into 2003. In the meantime, the frustrations for ourselves and our patients are likely to grow while at the same time new evidence on effectiveness is likely to widen the indications for emerging therapies for AMD including verteporfin therapy.

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