INTERNATIONAL ANATOLIA ACADEMIC ONLINE JOURNAL
e-ISSN 2148-3159 HEALTH SCIENCES RESEARCH ARTICLE

THE EFFECTIVENESS OF PHOTODYNAMIC THERAPY (PDT) WITH VERTEPORFIN IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION (ARMD) AND UNDERSTAND ALL FEATURES OF VERTEPORFIN FOR OBJECTIVE ADVISING TO UKRAINIAN PATIENTS*

Ayhan ÖNAL, *0000-0003-3637-0495*

Geliş Tarihi/Received	Kabul Tarihi/Accepted	Yayın Tarihi/Published
26.08.2022	29.08.2022	30.08.2022

Correspondence: *Ayhan ÖNAL, drayhanonal@yahoo.com*

*Bu makale yazarın uzmalık tezinden türetilmiştir.

Abstract

In this study a systematic review of the clinical effectiveness of PDT compared with current practice was undertaken. Searches in Macular degeneration Network, Investigative Ophthalmology and Visual Science, Medline, Embase-Elsevier, the Cochrane Library and the Internet, updated to January 2007, revealed the Treatment of ARMD with Photodynamic Therapy (TAP) and the Verteporfin in Photodynamic Therapy (VIP) fully published, and other few ongoing randomized controlled trials. The overall incidence of study eye adverse events was not significantly different between verteporfin and placebo. Verteporfin-treated patients did not experience development of more subretinal hemorrhage, fibrosis, or atrophy of the retinal pigment epithelium than did placebo-treated patients. No difference in VA between verteporfin-treated patients and controls was noted when the area of classic choroidal neovascularization (CNV) was more than 0% but less than 50% of the area of the entire lesion (termed minimally classic CNV lesions). However, minimally classic CNV lesions receiving verteporfin therapy were less likely to show progression of classic CNV beyond the area of the lesion at baseline, to have fluorescein leakage from classic CNV and to have a lesion size more than six disc areas compared to those receiving placebo. Verteporfin in combination with PDT should only be used by retinal specialists experienced in the management of ARMD and in diagnosis of classic CNV using fluorescein angiography (FA). Verteporfin in combination with photodynamic therapy may be used to treat patients with predominantly classic subfoveal CNV secondary to ARMD.

Keywords: Verteporfin and ARMD, exudative age-related macular degeneration and PDT with verteporfin, subfoveal ARMD and verteporfin

1. INTRODUCTION

Age-Related Macular Degeneration (ARMD), which is a disorder in the macula of the eye, causes progressive damage or deterioration that allows people to see straight ahead and read fine print [1] ARMD is usually classified as early or late. Late disease can be divided into atrophic (dry) and exudative (wet) forms [2]. About 80% to 90% of people with ARMD have the dry form. Estimates indicate that only 10% to 20% of all patients with any sign of ARMD have the neovascular form of the disease [30, 31]. Considerable vision loss can also result from features associated with non-neovascular ARMD, but serious vision loss occurs much more rarely than with neovascular ARMD. Neovascular ARMD accounts for approximately 90% of cases with severe vision loss, however [3].

Age-related macular degeneration (ARMD or AMD) is the leading cause of legal blindness (VA of 20/200 or worse) in developed, industrialized and the western countries for those over the age of 60-65 years [4-9]. It is estimated that 30% of the over-75-year-old age group is affected [10] An international survey found that only 2% of adults considered ARMD to be the leading cause of blindness among those older than 50 years, and 82% of those surveyed were not familiar with ARMD [11]. According to the World Health Organization (WHO), 8 million people have severe blindness due to ARMD, excluding the countries where data are scare [12].

Although increased age (senescence) is the principal risk factor, epidemiologic studies have found several other risk factors associated with ARMD, including environmental factors (long-term cigarette smoking, dietary fat intake), elevated levels of serum cholesterol, ischemia, oxidation {oxidative stress (free radicals)}, low level of antioxidants, elevated blood pressure (hypertension), cardiovascular disease, atherosclerosis, light exposure, iris color, race, and genetic predisposition (a positive family history) [4,13]. However, a recent animal model suggests an important role for the immune system in the development of ARMD [14].

ARMD is a slow, progressive and painless eye condition. But when it reaches the point of CNV, the loss of sharp, central vision needed to read street signs and fine print and to recognize faces can be sudden, severe, and irreversible. The eye can be compared to a camera, with the back of the eye, the retina, similar to the film. Because age is a significant risk factor for the development of ARMD, timely access to eye care may have preventive value [1].

Early diagnosis is critical to preserve vision and prevent additional loss. The disease usually manifests itself after age 50 years. The disease often is bilateral and patients report a significant history of disease in family members who have lived to later years of their life. Many patients develop a more rapid form of visual loss secondary to the development of neovascularization (NV) from the choroid that develops either below or above the RPE; this form of ARMD is referred to as "wet," while the more prevalent form is known as "dry." When the dry form of ARMD progresses with larger areas of RPE atrophy, the condition is referred to as GA. GA usually is bilateral but not necessarily symmetrical. It can develop NV and result in a more rapid loss of vision. Currently, no proven treatments are available for dry ARMD and previously, the only available treatment was laser photocoagulation (LP).

The two currently proven treatments are LP and PDT, but these measures are effective in only a small fraction of eyes with the exudative form of ARMD. Vision rehabilitation can help patients maximize their remaining vision and adapt so that they can perform activities of daily living. Families need encouragement in providing support and helping patients adjust to being partially sighted [15].

Verteporfin therapy is a relatively new technique involving PDT. Verteporfin (a benzoporphyrin derivative monoacid, BPD-MA) is a light-activated drug that has proved effective in reducing the risk of vision loss in selected patients with subfoveal neovascular ARMD [16-18]. One of the principal aims of verteporfin therapy for neovascular ARMD is to damage CNV selectively while preserving the adjacent normal choriocapillaris, RPE, and neurosensory retina. The goal is to avoid the absolute scotoma caused by LP and permit the treatment of a broader range of subfoveal CNV with respect to lesion size and initial VA [16,17]. Verteporfin therapy has now been approved by regulatory authorities in many countries, including the European Union (EU) and the US, and provides the means to treat neovascular ARMD in many patients whose condition was previously considered untreatable. If these patients are to benefit from treatment, it is vital that primary care physicians educate patients and make prompt referrals to an ophthalmologist, as needed [19].

In this study it was aimed to determine one of the most usable and effective medical treatment procedures in exudative ARMD, PDT with verteporfin and understand & evaluate the detailed safety profile of verteporfin in patients with subfoveal CNV caused by ARMD in Ukraine.

2. MATERIALS-METHODS

Randomized controlled trials were included where PDT using photosensitive drug, verteporfin was compared with no specific treatment, placebo, or laserphotocoagulation in adults with wet AMD. There was no restriction on outcomes, but information on visual acuity (VA), contrast sensitivity, quality of life, and side- effects of treatment were particularly sought. The searches on e-Medicine from Web-MD, Cochrane Library, American Academy of Ophthalmology (AAO), Blackwell Synergy, Retina International, Embase & Elsevier, AMD.org, Macular degeneration Network, conference abstracts (ARVO), Investigative Ophthalmology and Visual Science, Medline, and the Internet sites were updated to January 2007. Data extraction and quality assessment of included studies using the TAP study group 1999, 2001, and current reports related to the VIP ARMD trials, and other few groups & trials were done in duplicate.

3. RESULTS and DISCUSSION

The overall safety profile for verteporfin therapy was judged by the TAP and VIP Study Groups to be excellent, based on 3 masked, placebo-controlled trials in 948 ARMD patients treated and followed for 2 years (Table 1,2,3, 4,5), even though the average age of patients was 75 years at study entry. The larger effect size suggested by the subgroup analysis of the TAP trial was not mirrored by findings from VIP. The TAP subgroup findings reported here the basis for licensing the predominantly classic patient group and the VIP trial results the basis of being recently granted license for use in occult wet AMD [16-18,20].

The key result of the TAP and VIP trials indicates that PDT with verteporfin is more effective than placebo in terms of the primary outcome (loss of 15 letters or more of visual acuity) and it is very unlikely that this result is a chance finding. Furthermore, considering information on the other outcomes measured such as contrast sensitivity and side effects, the benefits seem to outweigh the harms so that PDT with verteporfin is effective overall in slowing the rate of vision loss. However, without information on effects of treatment on quality of life it is difficult to gauge the impact of treatment on patients. This set of findings is consistent with previous reviews and systematic reviews on this study [21-23].

For most body systems and individual adverse events, incidence was similar between verteporfin-treated and placebo-treated patients.

The allergic reactions that occurred in these trials were not considered to be related to verteporfin therapy by the treating ophthalmologists (Table 6). These reactions were attributed to other agents (e.g.; pollen, concomitant medications, and fluorescein) and were not temporally related to verteporfin therapy. It should be noted, however, that 1 severe allergic reaction (onset of dyspnea and flushing without itching during the infusion) was reported in a patient with pathologic myopia and is described specifically in VIP Report No. 1 [24,25]. Thus, although very rare, allergic reactions may occur and patients should be supervised during verteporfin infusion.

The mechanism of infusion-related back pain is unknown, and the event was rare, but it was clearly associated with verteporfin infusion in 15 patients (2.4%). A similar phenomenon of unexplained lower back pain has been reported for other intravenously administered drugs during infusion, including streptokinase [26] and liposomal agents [27-29]. The incidence of musculoskeletal pain (including back pain) during verteporfin infusion was recently reported to be higher (9.6%) than that reported in the TAP Investigation and VIP Trial (2.4% for infusion-related back pain). In this prospective, nonrandomized study, patients were directly asked if they were experiencing pain [30]. Verteporfin for injection is a lipid-based formulation, and it has been suggested that liposomes may activate the alternative complement pathway and the production of anaphylatoxins [31-34].This activation may lead to the back pain phenomenon, as well as to symptoms such as chest pain, dyspnea, and flushing, a varying constellation of events that have been noted in post-marketing safety surveillance data for verteporfin therapy (and consequently noted in the product prescription information), as well as for other liposomal agents[28,29]. This hypothesis of complement activation is supported by a recent small study that suggested that neutrophil margination, which was quickly reversible, was a possible mechanism for verteporfin infusion-related pain [35].

Visual disturbance (blurred vision, decreased VA, and visual field defects) events: Patients in the VIP ARMD Trial, most of whom had occult with no classic CNV and better VA at baseline (mean letter score of 66, or approximate Snellen equivalent of 20/50 +1) [18], reported a higher incidence of visual disturbance events (particularly decreased vision) than patients in the TAP Investigation, who had classic containing CNV and worse VA at baseline (mean letter score of 53, or approximate Snellen equivalent of 20/80 -2) [17]. Acute severe VA decrease (>4 lines within 7 days of therapy) was relatively uncommon, occurring in 11

patients in the VIP ARMD Trial (4.9%) and in 3 patients in the TAP Investigation (0.7%). Similar to overall visual disturbance events, acute severe VA decrease occurred more commonly in patients included in the VIP ARMD Trial. In that trial, the incidence of acute severe VA decrease associated with verteporfin therapy was higher than in the TAP Investigation, regardless of lesion composition. The 5% risk of acute severe VA decrease is outweighed by the net vision benefit of verteporfin therapy, which reduces the risk of moderate and severe VA loss (table 33-d-). As discussed elsewhere, the relatively good baseline VA score in the VIP ARMD Trial may have contributed to the higher incidence of this event in that trial [20]. Any visual disturbances, including acute severe VA decrease, also did not affect the overall vision outcome benefit associated with treatment, as shown in previously published reports of these individual trials [16-18], in which the risk of moderate and severe VA loss was less for verteporfin treated patients than placebo patients at both the Month 12 and Month 24 examinations. From a safety perspective, although verteporfin and placebo groups were balanced with respect to VA at baseline, the proportion of patients with severe VA impairment (_20/400 [VIP ARMD] or _20/500 [TAP]) 24 months after initiating therapy was notably lower in the verteporfin group compared with the placebo group (15% vs. 25% for patients who had occult with no classic CNV in the VIP ARMD Trial [18], and 6% vs. 13% in the TAP Investigation [16], for the verteporfin and placebo groups, respectively). Nevertheless, physicians need to highlight the risk of acute severe VA decrease while putting the risk in perspective with treatment benefits. Although the risk is small, acute severe VA decrease can affect vision profoundly and immediately. As described in another report that provided a detailed review of these cases, most but not all such events were associated with at least 3 lines of VA loss from baseline by the month 12 and month 24 examinations, although the average change in VA of these cases was similar to placebo-treated cases at these time points [20].

Because verteporfin is a light-activated drug, all patients who receive it become photosensitive for period of time related to the pharmacokinetic half-life of verteporfin and the time needed to eliminate the drug from skin and other tissues. Verteporfin has short half-life of 5 to 6 hours [19]. In the ARMD trials conservative photosensitivity precaution periods were implemented based on verteporfin’s half-life, as well as specific photosensitivity tests in other studies [36]: 48 and 24 hours in TAP and VIP, respectively, representing 8 and 4 times the half-life of verteporfin.

The event of gastrointestinal carcinoma appears in the U.S. prescription information for verteporfin therapy despite its low incidence (1.3% in the verteporfin group) and similar incidence with placebo (0.9%) after 2 years of study follow-up. Most of these events were colorectal cancer (1.0% of verteporfin-treated patients and 0.9% of placebo-treated patients), which is one of the most common malignancies in this age group and which increases markedly with advancing age [37].The annual incidence of colorectal cancer in the controlled ARMD studies is consistent with the natural annual incidence of colorectal cancer [37]. In addition, colorectal cancer develops with a natural history of 10 to 15 years [38].

Injection site reactions occurred with relatively high incidence in the first 12 months of the TAP Investigation in verteporfin-treated patients (13.4%) [17]. After analysis of the 12-month data showed that these events were common, additional precautions and training were instituted in the trials to try to reduce these events and avoid extravasation. These precautions included using the largest arm vein possible for the injection, establishing a free-flowing intravenous (IV) line before starting the verteporfin infusion, and monitoring the IV line carefully throughout the infusion. The precautions appeared to be associated with a reduced risk of subsequent injection site events, as the incidence of these events in the last 12 months of the TAP Investigation was much lower than in the first 12 months. Similar precautions were instituted soon after initiation of enrollment in the VIP Trial, and the incidence of injection site reactions in that trial was low [17].

The concentrated amount of verteporfin under the skin caused by extravasation could lead to a severe local burn if exposed to direct light. This precaution should be maintained as long as there is swelling or discoloration or any indication that verteporfin is still present in the area of extravasation [37].

The overall excellent safety profile for verteporfin therapy, as shown by these results from 3 randomized, placebo-controlled trials, has been confirmed by post-marketing surveillance data over 3 years (since April 2000, when verteporfin was approved for use in the U.S.) No additional, different safety problems have been identified beyond those identified in the randomized trials. Since April 2000, it is estimated that more than 200,000 patients have received at least one course of therapy [39].

The pattern of results in subgroups is odd. If predominantly classic ARMD is more aggressive and sight threatening and so more susceptible to PDT treatment, a gradient of

effect between 100% classic and 100% occult would be expected. The TAP subgroup analysis however suggests that occult has a similar effect size as predominantly classic, with minimally classic having a worse outcome than both. The VIP trial suggests a similar effect size in minimally classic as occult. For there to be a biologically plausible gradation of effect from pure classic to pure occult, the relative risk (RR) for occult would be near to or even greater than 1. This is incompatible with the actual result of the VIP trial in which the RR for occult only is 0.8. The statistical plan, in describing subgroup analysis a priori, makes no reference to biological plausibility, suggesting that this may have been arrived at post hoc. Furthermore, the description of the rationale for the subgroup analysis is in terms of assessing general consistency across the subgroup levels, rather than a targeted investigation to a very limited number of factors for which there was a high level of initial suspicion about presence of a subgroup effect. Also, before the TAP trial was published, the groups normally mentioned classic only, mixed (classic and occult), and occult only were. After the TAP trial was published, predominantly classic as a subgroup appeared; there is no mention of the term in Medline or Embase before this time. In fact two were obtained, but % classic and presence of occult are interdependent in the context of TAP because if one is statistically significant, the other will automatically be. It is essentially the same data expressed in a slightly different way, so effectively there was only one statistically significant result. Data across TAP and VIP are not consistent with the subgroup effect identified in TAP. At trial level (the level at which the studies were designed and carried out) there is relatively little difference in effect between TAP and VIP despite their very different patient populations. The results of ongoing trials [especially the VIM and VIO randomized clinical trials (RCTs)] should provide further data to create a more complete picture of the relationship between the nature of the lesion and effect size [16, 17, 18, 40-42].

4. CONCLUSION

Since verteporfin therapy of subfoveal CNV from ARMD can safely reduce the risk of vision loss, it is recommended verteporfin therapy for treatment of patients with predominantly classic CNV from ARMD. Verteporfin PDT is effective in reducing the visual deterioration associated with neovascular lesions in wet AMD. It should be noted that as far as treatment of wet AMD is concerned, verteporfin PDT is currently only licensed for those forms where classic neovascular lesions predominate. Whether this is an efficient use of healthcare resources is highly uncertain, but on balance it is believed that it is inefficient.

Other issues concerning implications to other parties, national targets, implementation and equity were identified, which may need to be considered in any decision on whether verteporfin PDT is funded by the National Health Service (NHS). Sources of uncertainty concerning efficiency could be reduced, and suggestions for further research are made. Principal among these is a large publicly funded pragmatic RCT with parallel health economic evaluation. Treatment of wet AMD with verteporfin, with other types of PDT, and with other new technologies are areas under very active investigation, so this technology should be kept under close review.

Verteporfin should only be used by retinal specialists experienced in the care of patients with age related macular degeneration, who are experienced in the diagnosis of classic CNV using fluoroscein angiography, these recommendations are supported by the Royal College of Ophthalmologists [43].

5. HIGHLIGHTS

• Verteporfin PDT is effective in reducing the visual deterioration associated with wet ARMD. This effect is statistically significant and clinically important.

• This benefit is achieved at some cost in terms of adverse events, but qualitatively at least, the balance between beneficial and harmful effects favors verteporfin PDT.

• Unfortunately the cost of verteporfin PDT is very high between at £850 [165] to £1181 per treatment and more than one treatment may be needed. Inevitably, efficiency, particularly its cost–utility becomes an important issue.

• There is uncertainty about the cost–utility of verteporfin PDT. Past estimates of cost per quality-adjusted life-year (QALY) at 2 years range from £60,000 to £122,000. The economic model developed as part of this report obtained a base-case estimate of between £151,000–182,000. The sensitivity analyses ranged from £342,000 to £47,000 (see also addendum).

• Favorable estimates of cost–utility have been obtained in past economic evaluations, but only by modelling the cost–utility beyond 2 years (the length of follow-up in the two included RCTs) and by basing the results of effectiveness on subgroup analyses of the TAP trial.

• It should be clearly noted that these estimates of cost–utility assume that it is the better-seeing eye which develops wet ARMD first. The efficiency of verteporfin PDT in a situation

where the worst-seeing eye develops ARMD cannot currently be considered but the efficiency of verteporfin PDT in this situation is likely to be even less favorable.

REFERENCES

1. 1. Freil JP (ed.) Dorland's Illustrated Medical Dictionary, 25th Edition, Philedelphia; 1974: 414-415.

2. Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, de Jong PT, Klaver CC, Klein BE, Klein R, et al. The international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group: Surv Ophthalmol 1995; 39:367 -74.

3. Kubo N, Ohno Y, Yanagawa H et al. Annual estimated number of patients with senile disciform macular degeneration in Japan. The Ministry of Health and Welfare in Japan. Tokyo, Japan: 1989, p 136.

4. Ambati, J. et al. (2003).An animal model of age-related macular degeneration in senescent Ccl-2- or Ccr-2-deficient mice. Nat. Med. 9, 1390–1397

5. Stone EM, Lotery AJ, Munier FL, et al: A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. Nat Genet 1999 Jun; 22(2): 199-202[Medline].

6. Alexander, Larry J. Primary Care of the Posterior Segment 2nd Ed. Appleton & Lange. 1994.

7. Kahn HA, Leibowitz HM, Ganley JP. The Framingham Eye Study, I: outline and major prevalence findings. Am J Epidemiol 1977 Jul; 106(1): 17-32[Medline].

8. Attebo K, Mitchell P, Smith W: Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. Ophthalmology 1996 Mar; 103(3): 357-64[Medline].

9. Mozaffarieh M, Sacu S, Wedrich A. The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: A review based on controversial evidence. Nutr J. 2003; 2: 20.

10. AMD Alliance International. Awareness research. Available at: http://www.amDALLIANCE.ORG/ amd/awareness research.html (accessed 1999).

11. World Health Organization. Fact sheet No. 144.Blindness and visual disability. Part III of VII: other leading causes worldwide. www.who.int/inf-fs/en/fact144html (accessed Dec 2002).

12. Pizzarello LD. The dimensions of the problem of eye disease among the elderly. Ophthalmology 1987; 94:1191–5.

13. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. Arch Ophthalmol 2000; 118:351-8.

14. Eagle RC: Mechanisms of maculopathy. Ophthalmology 1984 Jun; 91(6): 613-25[Medline].

15. American Family Physician 2000; 61:3035-42.

16. Bressler NM, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group: Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. Two-year result of 2 randomized clinical trials TAP report 2. Arch Ophthalmol 2001; 119: 198-207[Abstract/Free Full Text].

17. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of 2 randomized clinical trials—TAP report No 1.Arch Ophthalmol 1999; 117: 1329-1345.

18. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: Two year results of a randomized clinical trial including lesions with occult with no classic choroidal

neovascularization-Verteporfin in Photodynamic therapy report 2: Am. J Ophthalmol 2001; 131: 541-560.

19. Houle JM, Strong A. Clinical pharmacokinetics of verteporfin. J Clin Pharmacol 2002; 42:547–557.

20. Arnold JJ, Blinder KJ, Bressler NM, Bressler SB, Burdan A, Haynes L, Lim JI, Miller JW, Potter MJ, Reaves A, et al: Acute severe visual acuity decrease after photodynamic therapy with verteporfin: Case reports from randomized clinical trials—TAP and VIP report no. 3. Am. J Ophthalmol 2004; 137: 683-696.

21. Arnold JJ, Sarks H. Extracts from 'clinical evidence' Age related macular degeneration: BMJ 2000; 321:741–4.

22. Anon. Verteporfin in combination with laser therapy: helpful in some forms of age-related macular degeneration. Prescrire Int 2001; 10:78–81[Medline].

23. Wormald R, Evans J, Smeeth L, et al. Photodynamic therapy for neovascular age related macular degeneration. The Cochrane Library 2001; 2001:1–13.

24. Visudyne® (verteporfin for injection) [package insert]. Duluth, GA: Novartis Ophthalmics, Inc; 2002.Avaible at: http://www.qltinc.com/Qltinc/_downloads/commercial/US_Package_Insert.pdf: Accessed January 14, 2004.

25. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization pathologic myopia with verteporfin: 1 year results of a randomized clinical trial—VIP Report No. 1. Ophthalmology 2001; 108:841–852.

26. Lear J, Rajapakse R, Pohl J. Low back pain associated with streptokinase: Lancet 1992; 340: 851 (letter).

27. Sculier JP, Coune A, Brassinne C, et al. Intravenous infusion of high doses of liposomes containing NSC 251635, a water-insoluble cytostatic agent: A pilot study with pharmacokinetic data. J Clin Oncol 1986; 4:789 -797.

28. Hui YF, Cortes JE. Chest and back pain associated with a six-hour infusion of liposomal daunorubicin. Ann Pharmacother 2000; 34:810–811.

29. Skubitz KM, Skubitz AP. Mechanism of transient dyspnea induced by pegylated-liposomal doxorubicin (Doxil): Anticancer Drugs 1998; 9:45–50.

30. Borodoker N, Spaide RF, Maranan L, et al. Verteporfin infusion-associated pain. Am. J Ophthalmol 2002; 133:211–214.

31. Cunningham CM, Kingzette M, Richards RL, Alving CR, Lint TF, Gewurz H. Activation of human complement by liposomes: A model for membrane activation of the alternative pathway: J Immunol 1979; 122:1237–1242.

32. Chonn A, Cullis PR, Devine DV. The role of surface charge in the activation of the classical and alternative pathways of complement by liposomes: J Immunol 1991; 146: 4234–4241.

33. Devin DV, Wong K, Serrano K, Chonn A, Cullis PR. Liposome-complement interactions in rat serum: Implications for liposome survival studies. Biochim Biophys Acta 1994; 1191:43–51.

34. Szebeni J, Wassef NM, Rudolph AS, Alving CR. Complement activation by liposome-encapsulated hemoglobin invitro: The role of endotoxin contamination: Artif Cells Blood Substit Immobil Biotechnol 1995; 23: 355–363.

35. Spaide RF, Maranan L. Neutrophil margination as a possible mechanism for verteporfin infusion-associated pain. Am. J Ophthalmol 2003; 135: 549–550.

36. Houle JM, Strong HA: Duration of skin photosensitivity and incidence of photosensitivity reactions after administration of verteporfin: Retina 2002; 22: 691–697

37. American Cancer Society. Cancer Facts and Figures, 2002, Atlanta, GA: American Cancer Society, 2002. Available at: http://www.cancer.org/downloads/STT/CancerFacts&Figures2002TM.pdf: Accessed December 11, 2003.

38. Winawer SJ, Natural history of colorectal cancer. Am. J. Med. 1999; 106(1A): 3S–6S, 50S–51S.

39. Retina, the Journal of Retinal and Vitreous Diseases, 2004, Volume 24: 1-12

40. Blumenkranz MS, Bressler NM, Bressler SB, Donati G, Fish GE, Haynes LA, Lewis H, Miller JW, Mones JM, Potter MJ, et al. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: Three-year results of an open-label extension of 2 randomized clinical trials—TAP report no. 5. Arch Ophthalmol 2002; 120: 1307-1314.

41. TAP study group: Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration, additional information regarding baseline lesion composition's impact on vision outcomes, TAP report 3. Arch Ophthalmol 2002; 2002: 1443–54.

42. 186. Rubin GS, Bressler NM, TAP study group. Effects of verteporfin therapy on contrast sensitivity. Results from the treatment of age related macular degeneration with photodynamic therapy (TAP) investigation, TAP report 4. Retina 2002; 22: 536–44[CrossRef][Medline].

43. Royal College of Ophthalmologists: Guidelines for photodynamic therapy. August 2000: Cited at www.rcophth.ac.uk/publications/guidelines/photodynamic_therapy.html: 13.10.00.

Tables

Table 1: The results of included- studies

	TAP			VIP		
	PDT	Placebo	RR	PDT	Placebo	RR
Outcome at 2 years	n=402	n=207	(95% CI)	n=225	n=114	(95% CI)
Loss of 15 or more letters	47.0%	62.3%	0.75 (0.65 to 0.88)	53.8%	66.7%	0.81 (0.68 to 0.96)
Mean number of contrast sensitivity letters lost	1.3*	5.2*	Not applicable	Not reported		
	p<0.001 for difference					
Mortality	3.2%	3.9%	0.84 (0.35 to 2.0)	1.8%	2.6%	0.68 (0.15 to 3.0)
Severe visual loss (>20 letters) within 1 week	0.7%	0%	3.6 (0.19 to 70)	4.4%	0%	11 (0.63 to 110)
Adverse events associated with treatment	47.8%	33.8%	1.4 (1.1 to 1.8)	42.7%	18.4%	2.3 (1.5 to 3.5)
Injection site adverse events	15.9%	5.8%	2.8 (1.5 to 5.0)	8.0%	5.3%	1.5 (0.62 to 3.7)
Photo-sensitivity reactions	3.5%	0%	15 (0.9 to 250)	0.5%	0.9%	0.51 (0.03 to 8.0)

95% confidence intervals calculated from data presented in published papers.
*No standard deviation or other measure of spread given, p level as reported in published paper.

Table 2: Contrast Sensitivity Change at Month 12 (Ref: 1-c-) and Month 24 (Ref: 2-c-) Examination in the TAP Investigation and at Month 24 in the VIP Trial

	Contrast sensitivity letters lost		
Visit (Months)	Verteporfin (letters)	Placebo (letters)	*P*
*TAP Investigation: Total Patient Population**			
12	1.3	4.5	<0.001
24	1.3	5.2	<0.001
VIP Trial: Patients with Occult CNV with No Classic CNV			
12	3.6	4.4	0.164
24	3.7	6.1	0.004

* In an exploratory analysis of patients with predominantly classic CNV with occult CNV, the mean change in contrast sensitivity score from baseline was almost 0 at the month 24 examination in verteporfin-treated eyes compared with a decrease of approximately 6 letters (approximately two segments of contrast) in eyes receiving placebo.[3]

Table 3: Included RCT participant characteristics and follow-up

	TAP		VIP	
	Intervention	Control	Intervention	Control
N	402	207	225	114
Mean age (years)	74.9	76.0	75	74
Women (%)	53.2	62.8	58	62
White (%)	98.5	98.1	99	98
Mean visual acuity in treated eye	52.8 letters	52.6 letters	66 letters	65 letters
Mean visual acuity in fellow eye	48.9 letters	51.8 letters	44 letters	48 letters
Proportion with visual acuity > 73 letters in fellow eye (%)	36.3	38.2	27	29
Lesion area subfoveal (%)	89.1	90.3	85	81
Some classic component (%)	89.8	90.4	24	19
Some occult component (%)	75.9	75.8	93	96
Follow-up at 12 months (%)	94.3	93.7	93.3	91.2
Follow-up at 24 months (%)	87.3	86.0	85.8	86.8
Mean no. treatments per patient (1st year)	3.4	3.7	3.14	3.55
Mean no. treatments per patient (2nd year)	2.2	2.8	1.81	2.36
Mean no. angiographies per patient	Not given	Not given	Not given	Not given

Table 4: First-year safety and adverse events for TAP and VIP trials

	TAP		VIP	
	Verteporfin	Placebo	Verteporfin	Placebo
Total no. of patients	402	207	225	114
Mortality	8	4	NR	NR
Severe visual acuity loss within 1 week (loss of 20 letters)	NR	NR	NR	NR
Visual disturbance	71 (17.7%)	24 (11.6%)	NR	NR
Adverse event associated with treatment	185 (46.0%)	74 (35.7%)	NR	NR
Stopped treatment from adverse event	7 (1.7%)	0	NR	NR
Injection site adverse events	54 (13.4%)	7 (3.4%)	NR	NR
Allergic reactions	5 (1.2%)	7 (3.4%)	NR	NR
Photosensitivity reactions	12 (3.0%)	0	NR	NR

Table 5: Cumulative 2-year safety and adverse events for TAP and VIP trial

	Verteporfin	Placebo	Relative risk* (95% CI)	Verteporfin	Placebo	Relative risk* (95% CI)
Total no. of patients	402	207	0.84	225	114	0.68
Mortality	13 (3.2%)	8 (3.9%)	(0.35 to 1.99)	4 (1.8%)	3 (2.6%)	(0.15 to 2.97)
Severe visual acuity loss within 1 week (loss of 20 letters)	3 (0.7%)†	?0†	3.61 (0.19 to 69.62)	10 (4.4%)	0	10.69 (0.63 to 108.75)
Visual disturbance	89 (22.1%)	32 (15.5%)	1.43 (0.99 to 2.07)	94 (41.8%)	26 (22.8%)	1.83 (1.26 to 2.66)
Adverse event associated with treatment	192 (47.8%)	70 (33.8%)	1.41 (1.14 to 1.75)	96 (42.7%)	21 (18.4%)	2.32 (1.53 to 3.51)
Stopped treatment from adverse event	7 (1.7%)	0	7.74 (0.44 to 134.90)	8 or 9† (3.6% or 4.0%)	0 or 1‡ (0.6% or 0.9%)	9.67 (0.57 to 164.65)
Injection site adverse events	64 (15.9%)	12 (5.8%)	2.75 (1.52 to 4.97)	18 (8.0%)	6 (5.3%)	1.52 (0.62 to 3.72)
Allergic reactions	8 (2.0%)	8 (3.9%)	1.37 (0.37 to 5.12)	3 (1.3%)	3 (2.6%)	0.51 (0.10 to 2.47)
Photosensitivity reactions	14 (3.5%)	0	14.97 (0.90 to 249.68)	1 (0.5%)	1 (0.9%)	0.51 (0.03 to 8.03)

* *Calculated using Review Manager software version 4.1*
† *TAP trial data mentioned in VIP trial report discussion section*
‡ *Unclear from VIP trial report whether one patient was in the treatment or placebo arm*

Table 6: Hepatic Impairment and Verteporfin Therapy (Ref: 25-c-)

- Mild hepatic impairment usually includes transaminase levels up to 5 times the upper normal limit and bilirubin levels up to 1.5 times the upper normal limit.
- The pharmacokinetic properties of verteporfin have been investigated in subjects who had transaminase levels up to 3 times the upper limit of normal and normal bilirubin levels. There were no significant differences in the pharmacokinetic properties between normal subjects and mildly hepatically-impaired subjects.[25]
- Verteporfin therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since there has been no experience in these patients.

Table 7: Utilities and probabilities for visual acuity at 24 months for PDT and BSC (inputs to WMHTAC model).

Change in visual acuity (lines)	Mean utility score	PDT probability	BSC probability
≥ 6-line increase	0.89	0.008	0
≥ 3-line to < 6-line increase	0.81	0.080	0.038
≥ 1- line to < 3-line increase	0.81	0.065	0.062
No change	0.57	0.147	0.126
≥ 1-line to < 3-line decrease	0.52	0.229	0.150
≥ 3-line to < 6-line decrease	0.52	0.289	0.324
≥ 6-line decrease	0.40	0.182	0.300