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實 EVIDENCE 証

Hospital Authority Head Offi *al Effectiveness Unit*
Medical Services Development Division *Issue 14, 2001*

▪ Chronic bronchitis patients on long-term mucolytic had fewer exacerbations than on placebo

There are regional variations in prescribing mucolytic to chronic bronchitis patients. They are widely used in some European countries but not so in UK, USA and Australia, where mucolytic are generally perceived to be ineffective[1,2,3]. '實 **EVIDENCE** 証' presents two recent meta-analyses of randomised controlled trials (RCTs) that favour the long-term use of mucolytic in chronic bronchitis patients.

A systematic review by the Cochrane group was recently updated on 17 Jan 2000[4]:

Problem/patient	Adults with chronic bronchitis (as defined by the criteria of the American Thoracic Society, European Respiratory Society, WHO or the British MRC).
Intervention	N-acetylcysteine (NAC), S-carboxymethylcysteine, bromhexine, ambroxol, sobrerol, cithiolone, letosteine and iodinated glycol.
Comparison	Comparison with placebo for at least 2 months
Primary outcomes	(i) Number of acute exacerbations; (ii) number of days of disability; (iii) number of days on antibiotics.

22 RCTs met review selection criteria, meta-analysis showed that treatment with mucolytic was associated with a small reduction in acute exacerbations and a somewhat greater reduction in total number of days of disability.

i) A weighted mean reduction of 0.067 exacerbations per month (95%CI -0.079 to -0.055, $p < 0.0001$). With a control rate of 2.7 exacerbations per year, long-term mucolytic treatment could reduce 1 exacerbation in approximately 15 months.

ii) A weighted mean reduction of 0.56 day of disability per patient per month (95%CI -0.77 to -0.35, $p < 0.0001$), and a corresponding reduction of 0.53 day on antibiotics per patient per month (95%CI -0.76 to -0.31, $p < 0.0001$).

iii) More patients in the mucolytic group than in the placebo group remained exacerbation-free (OR 2.22, 95%CI 1.93 - 2.54, $p < 0.001$).

iv) No difference in lung function or in adverse effects between treatment and control.

In the second systematic review[5], the authors searched MEDLINE, EMBASE, Cochrane Library and bibliographies (with no language restriction) for published RCTs on:

Patient	Patients with chronic bronchitis
Intervention	Oral N-acetylcysteine (NAC)
Comparison	Placebo
Outcomes	(i) Prevention of exacerbations (cough, sputum volume or purulence, dyspnoea) (ii) Patient self-assessment of treatment efficacy (iii) Adverse effects ("dyspepsia, heartburn or diarrhoea", and withdrawal)

11 randomised trials published between 1976 - 1994 met preset criteria for review. 9 of 11 RCTs used the MRC definition of chronic bronchitis and nearly all participants were smokers. 2,500 patients were randomised to NAC (400-600 mg a day in two or three oral doses) or placebo for 12-24 weeks. Meta-analysis on information of 2,011 participants (not by intention to treat due to dropouts) shows:

	No. of RCTs	Treatment		Relative benefit (95%CI)	ARR	NNT
		NAC	Placebo			
Prevention of exacerbations	9	351/723 (48.5%)	229/733 (31.2%)	1.56 (1.37-1.77)	0.173	5.8 (95%CI 4.5-8.1)
Patient self-assessment of treatment efficacy	5	286/466 (61.4%)	160/462 (34.6%)	1.78 (1.54-2.05)	0.268	3.7 (95%CI 3.0-4.9)
Gastrointestinal adverse effects		68/666 (10.2%)	73/671 (10.9%)	1.0 (0.7-1.3)	-	-
Withdrawal		79/1207 (6.5%)	87/1234 (7.1%)	0.9 (0.7-1.2)	-	-

[Source:

1. *The COPD Guidelines Group of the Standards of Care Committee of the British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997 Dec;52(Suppl. 5):S1-28.*
2. *American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995 Nov;152(5Pt2): S77-121.*
3. *Thoracic Society of Australia and New Zealand. Guidelines for the management of chronic obstructive pulmonary disease. Mod Med Aust 1995;38:132-46.*
4. *Poole PJ, Black PN. Mucolytic agents for chronic bronchitis. In: The Cochrane Library [Online], Issue 3, 2001. Oxford: Update Software.*
5. *Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. Eur Respir J 2000 Aug;16(2):253-62.]*

- **RCT demonstrated effectiveness of photodynamic therapy (PDT) in slowing visual deterioration in subfoveal choroidal neovascularization (CNV) relating to aged-related macular degeneration (AMD)**

Two-year results from the TAP[1,2,3] (Treatment of Age-related macular degeneration with Photodynamic therapy) and VIP[4] (Verteporfin in Photodynamic therapy) trials (multicenter, randomised, double-masked and placebo controlled) found that PDT **with verteporfin** reduced the risk of disease progression and serious visual acuity loss (defined as > 3 and 6 lines loss) in patients who have subfoveal CNV relating to AMD if:

i) classic CNV occupies ≥50% of the area of the entire lesion (termed predominately classic CNV lesions)[1,2].

ii) occult with no evidence of classic CNV, together with evidence presumptive of recent disease progression: deterioration (visually or anatomically) within last 3 months or haemorrhage from the CNV lesion[4].

TAP trial (report 1 and 2)[1,2]

Inclusion criteria:

i) AMD-related subfoveal CNV
ii) Fluorescein angiography demonstrates evidence of classic CNV
iii) ≥50% of the total neovascular lesion (by area) is composed of CNV
iv) Neovascular lesion ≤5400 μm in greatest linear dimension
v) Best corrected visual acuity of 73 through 34 letters (Snellen equivalent of approximately 20/40 through 20/200)
vi) Age ≥50

Participants:

609 eyes (one eye per patient) were randomly assigned to treatment (n = 402) or placebo (n = 207) in a 2:1 ratio study design.

Follow-up:

Follow up 3 monthly and retreat with assigned regimen if fluorescein angiography shows leakage.

Outcomes:

i) At each follow-up from month 3 to 24, the verteporfin-treated group had better visual acuity, contrast sensitivity, and fluorescein angiographic outcomes than placebo-treated group. It also required fewer treatments than the placebo group (5.6 vs. 6.5 in 24 months).

Table 1. Visual acuity changes at month 3, 12 and 24:

	At month 3		At month 12		At month 24	
	Verteporfin	Placebo	Verteporfin	Placebo	Verteporfin	Placebo
≥6-line increase	0.2%	0.0%	1.0%	0.0%	0.8%	0.0%
≥3-line to < 6-line increase	2.0%	1.4%	5.0%	2.4%	8.2%	3.9%
≥1-line to < 3-line increase	15.4%	10.6%	10.4%	4.8%	6.5%	6.3%
No change	32.8%	32.4%	21.6%	16.4%	14.7%	12.6%
≥1-line to < 3-line decrease	31.3%	26.6%	23.1%	22.7%	22.9%	15.0%
≥3-line to < 6-line decrease	13.7%	17.9%	24.1%	30.0%	28.9%	32.4%
≥6-line decrease	4.5%	11.1%	14.7%	23.7%	18.2%	30.0%
Mean visual acuity loss (lines)	1.2	2.0	2.2	3.5	2.7	3.9
Wilcoxon rank sum test	P = 0.007		P < 0.001		P < 0.001	

The Kaplan-Meier curve (event rate analysis) showed that the verteporfin-treated group had consistently lower risk of visual acuity loss of ≥3 lines and ≥6 lines than placebo-treated eyes at every follow-up throughout the whole study period. The mean visual acuity loss at month 12 and 24 was statistical significantly different between treatment and placebo ($p < 0.001$).

ii) Subgroup analyses found:
- No attribute in which placebo treatment flared better than verteporfin treatment.
- Treatment benefit in terms of < 15 letters visual acuity loss (primary outcome) was confined to those eyes with classic CNV occupying ≥50% of lesion area, and in particular with no occult CNV:

	Visual acuity loss < 15 letters at month 12				Visual acuity loss < 15 letters at month 24			
	Verteporfin	Placebo	P_1	P_2	Verteporfin	Placebo	P_1	P_2
Classic CNV: ≥50% of lesion area	67.3%	39.3%	< 0.001	0.004	59.1	31.3%	< 0.001	0.02
Classic CNV: > 0 to < 50%	55.9%	55.3%	0.92		47.5%	44.2%	0.58	
Classic CNV: 0%$^{\Phi}$	63.2%	31.6%	0.02		56.1%	30.0%	0.06	
Occult CNV	56.4%	51.6%	0.33	< 0.001	47.7%	40.8%	0.16	< 0.001
No occult CNV	76.6%	30.6%	< 0.001		69.9%	28.6%	< 0.001	
Classic CNV ≥50% & no occult CNV	77%	27%	< 0.001					
Classic CNV ≥50% & occult CNV	55%	53%	0.80					

P_1 = χ^2 test for treatment effect within subgroups; P_2 = logistic regression for interaction between subgroups;
$^{\Phi}$ = Small sample size, n = 38 (treatment) vs. 19 (placebo)

VIP trial report 2[4]

Inclusion criteria:

i) AMD-related subfoveal CNV
ii) ≥50% of the total neovascular lesion (by area) is composed of CNV
iii) Neovascular lesion ≤5400 μm in greatest linear dimension
iv) If evidence of classic CNV, then visual acuity letter score more than 70
v) If no evidence of classic CNV, then evidence presumptive of recent disease progression: deterioration (visually or anatomically) within last 3 months or hemorrhage from the CNV lesion
vi) Best corrected visual acuity of at least 50 (Snellen equivalent of approximately 20/100 or better)

Participants:

339 eyes were randomly assigned to treatment (n = 225) or placebo (n = 114) in a 2:1 ratio. Of these, 258 eyes had occult-no-classic CNV, 166 were assigned to treatment and 92 to placebo.

Follow-up:

Follow up 3 monthly and retreat with assigned regimen if fluorescein angiography shows leakage.

Outcomes:

i) PDT with verteporfin reduced risk of visual acuity loss of ≥15 and 30 letters. This achieved statistical significance at month 24 but not at month 12 (for the entire study group and the subgroup of 'occult-no-classic CNV').

Table 3. Mean visual acuity changes during study

Visual acuity loss	Entire study group			Occult-no-classic CNV subgroup		
	Verteporfin	Placebo	P	Verteporfin	Placebo	P
≥ 15 letters at month 12	51%	54%	0.52	51%	55%	
≥ 15 letters at month 24	54%	67%	0.023	55%	68%	0.032
≥ 30 letters at month 24	30%	47%	0.001	29%	47%	0.004

Table 4. Detail breakdown of visual acuity changes of the 'occult-no-classic' subgroup

Visual acuity changes	At month 12		At month 24	
	Verteporfin	Placebo	Verteporfin	Placebo
≥3-line to < 6-line increase	3.0%	2.2%	4.8%	1.1%
≥1-line to < 3-line increase	9.0%	5.4%	7.8%	4.3%
No change	21.7%	16.3%	15.1%	15.2%
≥1-line to < 3-line decrease	15.1%	20.7%	17.5%	10.9%
≥3-line to < 6-line decrease	28.9%	22.8%	25.9%	21.7%
≥6-line decrease	22.3%	32.6%	28.9%	46.7%
Mean visual acuity loss (lines)	3.1	4.1	3.8	5.1
Wilcoxon rank sum test	P = 0.10		P = 0.006	

ii) Other secondary outcomes (size of lesion, development and progression of classic CNV) also favored verteporfin treatment significantly at month 12 and 24 (for the entire study group and the 'occult-no-classic CNV' subgroup).

iii) **Further** subgroup analysis within the 'occult-no-classic CNV' group suggested that treatment benefit was confined to eyes with either smaller lesion (≤4 disc areas) or lower levels of visual acuity with Snellen equivalent of $20/50^{-1}$ or worse:

Visual acuity loss at month 24 / Further subgroup attributes	≥ 15 letters			≥ 30 letters		
	Verteporfin	Placebo	P	Verteporfin	Placebo	P
Visual acuity ≤$20/50^{-1}$ **or** lesion ≤4 disc areas	49%	75%	< 0.001	21%	48%	< 0.001
Visual acuity ≥$20/50^{-1}$ **and** lesion > 4 disc areas	72%	52%	0.09	51%	41%	0.4

[Source:

1. *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 1. Arch Ophthalmol. 1999 Oct;117(10):1329-45.*
2. *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 results of 2 randomized clinical trials – TAP report 2. Arch Ophthalmol. 2001 Feb;119(2):198-207.*
3. *Wormald R, Evans J, Smeeth L, Henshaw K. Photodynamic therapy for neovascular age-related macular degeneration. In: Cochrane Library [Online], Issue 3, 2001. Oxford: Update Software.*
4. *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 May;131(5):541-60.]*

[***Editor's note:***

i) Please see original reports for description of adverse events.

ii) The TAP and VIP trials were sponsored by pharmaceutical companies and a number of investigators declared conflicts of interests involving in the manufacture of laser technology.

iii) Evidence though promising is limited, both in sample size and duration of follow up, such that rare adverse events could not be reliably assessed. Long-term efficacy and safety are therefore not yet known.

iv) Some conclusions were based on subgroup analysis.

v) The optimal follow up and treatment regimen has not been established.

vi) There is no published data on treatment impacts from the patient's perspective.

vii) The role of PDT with verteporfin in CNV from other causes such as angioid streaks, idiopathic, and presumed ocular histoplasmosis syndrome is still under investigation.]