Cases of visual field defect attributed to treatment with vigabatrin in prescription event monitoring study 1991-4 and long term follow up study 1998-9

	No (%) cases
Prescription event monitoring study	
Questionnaires sent	17 307 (100)
Questionnaires returned	11 769 (68)
Questionnaires with clinical data	10 178 (59)
Questionnaires with clinical data, for living patients	10 033 (58)
In these 10 033 living patients:-	
Patients with objective evidence of visual field defect	4 (0.04)
Long term follow up study	
Questionnaires sent for patients taking vigabatrin at end of prescription event monitoring study	7 228 (100)
Questionnaires returned	6 809 (94)
Questionnaires with clinical data*	5 074 (70)
Questionnaires with clinical data, for living patients	4 741 (66)
In these 4741 living patients:	
Objective evidence of visual field defect	36 (0.8)
Visual field defect "probably" associated with vigabatrin	14 (0.3)
Visual field defect "possibly" associated with vigabatrin†	16 (0.3)

*Patients no longer registered with general practitioner=1136; blank questionnaires or duplicate patients=599.

†Includes one case from the prescription event monitoring study.

clinical data (1735) or the patients had died (333). In the surviving 4741 patients, 89 reports were followed up with ophthalmologists.

The ophthalmologists consider that 30 (83%) of the 36 cases for which there is objective evidence of visual field defect are probably or possibly related to vigabatrin. In four cases they did not know whether the defect was related to vigabatrin treatment, and in the remaining two cases the defect was considered not to be due to vigabatrin. The mean age at the time of diagnosis for the 19 men was 45.7 years (range 20-64), and for the 11 women it was 37.6 years (range 20-56). The mean duration of treatment to time of diagnosis in these 30 cases was 66.3 months (range 33-96).

In this second study information was requested on events reported after the original questionnaire was returned. One of the original four cases is also included in the 30 cases of the current study because

visual field tests were carried out after the original questionnaire had been returned. In these two studies, 33 cases of visual field defect considered by ophthalmologists to be probably or possibly related to vigabatrin were identified, giving an incidence risk of 7.0 per 1000 patients (33/4741). The minimal risk, based only on cases considered probably due to vigabatrin, is 3.4 per 1000 patients (16/4741).

Comment

Although publicity bias may have influenced the number of patients referred for visual field tests since the original study,¹⁻⁴ this substantial increase in the number of confirmed cases of visual field defect attributed to vigabatrin shows the clinical importance of this lesion in the long term use of vigabatrin. We have also shown that signals of long latency adverse drug reactions identified in a prescription event monitoring study can be successfully investigated in a long term follow up study.

We thank all the general practitioners and hospital doctors who have taken part in these two studies. We also thank Jackie Barfoot for her help in coordinating the study.

Contributors: LVW participated in the study design and the follow up questionnaire, was responsible for the execution and coordination of the study, analysis and interpretation of data, and writing the short report. MDBS identified and validated the original cases, participated in formulating the design of the follow up study and the questionnaire, and contributed to writing the paper. RDM participated in study design and interpretation of results and edited the short report. RDM will act as guarantor.

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Association of variant alleles of mannose binding lectin with severity of pulmonary disease in cystic fibrosis: cohort study

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Prognosis of cystic fibrosis is conditioned by the severity of pulmonary damage, which is related to infectious complications. The group of $\Delta F508$ homozygous patients with cystic fibrosis shows a substantial variability in clinical expression of the severity of lung disease, which could be explained by the influence of modulating genes¹ that are probably related to the efficiency of host immune factors in fighting against infection in patients' lungs.

Mannose binding lectin, a protein of the innate immune system, is involved in opsonisation and phagocytosis of micro-organisms. The mannose binding lectin gene shows three major allelic variants

that are responsible for a decrease of the protein plasma concentration, an opsonic defect, and a common immunodeficiency.²

We investigated the possible modulating role of mannose binding lectin because studies have shown (a) that homozygosity or compound heterozygosity for mannose binding lectin variant alleles predisposes to recurrent infections including lung infections and (b) that *Staphylococcus aureus* and *Pseudomonas aeruginosa*—the two most common and deleterious pathogens found in lung infections in patients with cystic fibrosis—have been cultured from patients deficient in this gene.³⁻⁴

Subjects, methods, and results

We studied the association between the allelic variants of mannose binding lectin and phenotypical criteria describing the severity of pulmonary disease, such as spirometric measurement of forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), and bacteriological examination of the sputum.

To avoid any phenotypical heterogeneity as a result of allelic heterogeneity in the cystic fibrosis transmembrane regulator gene, we identified, in association with the National Observatory for Cystic Fibrosis, the homogenous $\Delta F508$ homozygous population with cystic fibrosis from adult and pediatric respiratory hospital units in France. The DNA of 164 patients was genotyped by means of denaturing gradient gel electrophoresis.⁵ We identified 11 patients homozygous or compound heterozygous for mutations of mannose binding lectin (mean (SD) age 19.0 (11.1) years). To avoid the influence of sex and age factors, each of these patients was paired with the patient of the same sex with wild type alleles of mannose binding lectin who was the closest in age from the whole population of 164 patients (mean (SD) age of the 11 controls 20.8 (10.4) years). Paired *t* test and McNemar test were then performed to compare these two groups.

Analysis of the data shows a significant decrease in FEV₁ and FVC values in the group of patients homozygous or compound heterozygous for mutations of the mannose binding lectin gene compared with the group of patients homozygous for its wild type allele (table). In addition, we observed a higher frequency of colonisation by *P aeruginosa* in patients homozygous for mutated alleles of the mannose binding lectin gene than in patients with its wild type alleles, although the value was not significant in the studied population. Data for patients heterozygous for the mannose binding lectin gene are not significant and require further studies on a larger group.

Comment

The data show that the gene product of mannose binding lectin behaves as a modulating factor of the respiratory involvement in cystic fibrosis and that alleles of the protein's mutants are associated with earlier degradation of pulmonary function in $\Delta F508$ homozygous patients with cystic fibrosis. The changes in the values of the res-

Clinical markers split by mannose binding lectin genotype

Variable	Mannose binding lectin genotype		Mean difference	95% CI	P value
	Wild type (n=11)	Homozygous or compound heterozygous (n=11)			
Mean FEV ₁ (% predicted)	75.7	46.8	28.9	2.5 to 55.3	0.04*
Mean FVC (% predicted)	88.8	63.2	25.6	1.1 to 52.5	0.05*
% positive for <i>P aeruginosa</i>	36.3	81.8			0.08†

*Paired *t* test. †McNemar test with Yates correction. Clinical data for the 164 subjects in the study are as follows: mean FEV₁=63.2; mean FVC=77.4; % positive for *P aeruginosa*=51.5. Nearly half of the population comes from adult centers.

piratory variables between the patient groups ($\geq 30\%$ for FVC and FEV₁) are high, which suggests that these effects are clinically relevant.

These results may also have clinical implications. Screening for patients with cystic fibrosis with deficient activity of mannose binding lectin would permit the identification of people in whom an increased risk of pulmonary infection may lead to a greater alteration of the respiratory function. These patients should benefit from a more intense follow up and adapted clinical care.

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Contributors: MG, JF, and CB designed this study. MG and CB were responsible for the genotyping analysis. MGB and JF handled the clinical data through the Cystic Fibrosis National Observatory and were responsible for the statistical analysis. MG, JF, and CB analysed and interpreted the data, wrote and revised the paper. CB and JF will act as guarantors.

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