Patients' characteristics according to treatment group

	α -IFN (n=12)	Placebo (n=12)
Age (y)	67.5 (61.5-74.5)	67.5 (66-73.5)
Male sex	6 (50)	10 (83)
Patients never previously treated	7 (58)	6 (50)
Duration of neuropathy (y)	3 (2-10)	3.5 (1-9.5)
Patients with bone marrow lymphoid infiltrate	2 (17)	1 (8)
Clinical score:		
M0	34 (25.5-35.5)	30 (25.5-36.5)
M3	28 (21-35)	28 (21.5-33)
M6	31 (27.5-35)	28 (24-31)

Values are median (25th-75th percentiles) or n (%).

The randomisation procedure resulted in balanced treatment groups for patient characteristics and neurological abnormalities (table).

Three patients in the α -IFN group withdrew from treatment, two because of side effects (one at day 30 for diarrhoea and one at day 60 for influenza symptoms) and one at day 60 because of worsening of the neuropathy. No patients had to stop treatment because of haematological toxicity.

The mean CNDS did not change significantly in either group: in the α -IFN group, it moved from 31.4 at baseline to 28.5 at 6 months, in the placebo group from 30.3 at baseline to 27.8 at 6 months. The absolute differences were close in the two randomised groups—namely, 1.8 in the α -IFN group and -2.5 in the placebo group ($p=0.84$) and the relative differences were also close (-6% v -6.5% respectively, $p=0.79$). In both groups, three out of 12 patients (25%) had improvement in CNDS of more than 20% ($p=1.00$). Electrophysiological data were available in nine patients treated with α -IFN and in 11 patients treated with placebo and did not detect significant improvement (data not shown).

In this double blind study of α -IFN versus placebo, we did not confirm the efficacy of α -IFN in peripheral neuropathy associated with a monoclonal anti-MAG IgM as suggested in a preliminary phase II open study.¹⁴ This discrepancy is not easy to explain. The mean baseline neurological scores, the number of patients previously treated, and the disease duration were the same in the two studies. However, both studies dealt with small cohorts. We think that the effect found in our preliminary study could have been amplified by the enthusiasm of physicians and patients in favour of interferon, a new therapeutic strategy at that time in neurological diseases, given that the trial was not blind. Both physicians and patients knew that it was not a placebo group. Interestingly, in our preliminary study, the decrease of the CNDS was mainly due to improvement in sensory symptoms (most of them subjective) and to subjective assessment by the patient. Moreover, we could not elucidate the potential mechanism of action of α -IFN as neither the level of monoclonal IgM, nor the anti-MAG antibody activity was modified.

In conclusion, these disappointing results of α -IFN in monoclonal IgM associated neuropathy point out to the need of double blind randomised studies versus placebo in neurological diseases where sensory symptoms are predominant. In monoclonal IgM associated neuropathy, new strategies leading to eradication of the B cell clone secreting monoclonal IgM, such as the use of fludarabine¹⁵ or anti-B cell monoclonal antibodies,¹⁶ should be tested in further studies.

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Reversible posterior leukoencephalopathy syndrome induced by granulocyte stimulating factor filgrastim

Posterior leukoencephalopathy syndrome is characterised by visual disturbances, altered mental status, drowsiness, seizures, headache, and occasionally focal neurological signs. It is usually associated with severe hypertension and has most often been seen in patients treated with immunosuppressive drugs such as cyclosporin A, tacrolimus, and interferon- α .^{1,2}

The granulocyte and granulocyte macrophage stimulating factor filgrastim (Neupogen®) is used in chemotherapy induced bone marrow suppression. By contrast with molgramostim (Leukomax®) filgrastim is supposed to have fewer CNS side effects. Intracranial hypertension and convulsions have been reported after molgramostim therapy. Only one case of recurring encephalopathy and focal status epilepticus due to filgrastim is published.³ In that case the contrast enhanced CT was normal.

We report a case of reversible posterior leukoencephalopathy syndrome with transient bilateral changes in the occipital and parietal regions involving the white matter on MRI induced by filgrastim. This is to our knowledge the first with reversible changes on MRI to be reported after filgrastim therapy.

A 45 year old previously healthy woman was diagnosed with centrocytic centroblastic non-Hodgkin's lymphoma with intermediate to high malignancy in August 1999. The first cycle of chemotherapy with vincristin, ifosfamide, and etoposid was well tolerated. Two days after termination of chemotherapy she received subcutaneously 300 μ g filgrastim (Neupogen) daily because of bone marrow suppression with leukopenia for 9 days. After 3 days the dose was increased to 600 μ g/day. One day after termination of filgrastim and almost 2 weeks after chemotherapy, she developed acute cortical blindness within 30 minutes. On the next day simple partial and complex partial seizures, non-convulsive status, agitation, and desorientation followed. Brain MRI obtained 1 day later showed bilateral hyperintensities in the parietal and occipital regions involving white matter with some involvement of the overlying grey matter on proton density images (figure). Non-convulsive status with somnolence and disorientation were documented by EEG, which showed a bilateral parieto-occipital focus with continuous rhythmic delta

Left: bilateral PD hyperintensities in the parietal and occipital regions at the onset of symptoms. Right: bilateral PD hyperintensities in marked resolution 7 days later.

activity, sharp waves, and spike wave complexes; status could be terminated with 1 mg intravenous clonazepam.

Lumbar puncture and ultrasonography of the vertebral and basilar arteries did not show any abnormalities. Transoesophageal echocardiography showed normal left ventricular function. Routine biochemistry including electrolytes, creatinine, and blood urea nitrogen were normal throughout except increased C reactive protein (due to tumour). Haematological values showed pancytopenia. There was no evidence for viral and bacterial infection. A pleural effusion on the left side had developed before chemotherapy. A chest radiograph was now normal. Blood pressure was normal throughout.

As no other diagnosis could be ascertained, a causal relation with filgrastim, her sole new medication, was discussed. The patient was treated with a diuretic (furosemid), a neuroleptic (haloperidol), and anticonvulsants (phenytoin and clonazepam intravenously). The syndrome gradually remitted after 1 week without residue. The patient was well thereafter. Control MRI 7 days after the onset of symptoms showed hyperintensities in the parietal and occipital regions involving white matter in marked resolution on proton density images (figure).

This case demonstrates that the granulocyte stimulating factor filgrastim can have marked neurotoxic side effects in the form of a typical posterior leukoencephalopathy syndrome in the absence of severe hypertension. The pathogenesis of posterior leukoencephalopathy syndrome has remained illusive. It

probably reflects the increased vulnerability of posterior regions of the brain to different vascular, toxic, or metabolic disturbances. It has been suggested that the predelection for the posterior circulation is a consequence of poorer control of local cerebral autoregulation due to the relatively poorer sympathetic innervation. It cannot be stated whether in this case filgrastim neurotoxicity was due to direct toxic or transient vascular damage, by analogy with CNS toxicity reported after interleukin-2 therapy.^{4,5} Both mechanisms seem possible.

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Acute adverse reaction to fentanyl in a 55 year old man

We report an acute drug induced adverse reaction to fentanyl that was not immediately recognised as such. A 55 year old police officer was given a small dose of diazepam (5 mg) and fentanyl (0.05 mg) for the treatment of left chest pain. Immediately after receiving the medication, the patient developed acute confusion, intermittent somnolence, and stupor, and fluctuating tetraparesis. Before the onset of symptoms, no relevant hypoxia or hypoglycaemia were found. Pre-existing medication consisted of 20 mg amitriptyline and 1000 mg metformin a day. On initial examination, the most obvious symptoms included profuse sweating, bilateral miosis (pinpoint pupils), and severe generalised myoclonus predominantly affecting the face. Babinski's sign was negative on both sides. The patient showed severe fluctuating tetraparesis. Investigation of the cranial nerves showed no abnormalities. On admission in our institution, the patient immediately underwent intubation and artificial ventilation for suspected pulmonary aspiration. Thiamin was started at 100 mg thrice daily. Myocardial infarction and dissection of the aorta were ruled out. The previously given dosage of fentanyl and diazepam did not seem to explain the current neurological condition of the patient. The symptoms of disturbance of consciousness, hemiparesis, generalised myoclonus, and pinpoint pupils pointed to brainstem injury. To rule out basilar artery thrombosis, CT angiography was performed. There were no pathological findings in the brainstem or the basilar artery.

Transcranial Doppler ultrasound and sensory evoked potentials were normal. The EEG under sedation with midazolam and fentanyl showed intermittent bilateral synchronised frontal delta rhythms. Systolic blood pressure was slightly increased, between 140 and 180 mm Hg. Due to the patient's development of pneumonia, artificial ventilation was continued, and further sedation was given with fentanyl/midazolam. Sedation was continued for 72 hours, with an infusion of fentanyl (0.157 mg/h) and midazolam (3.3 mg/h) for ventilation therapy. After sedation was stopped, the distinctive neurological symptoms abruptly improved. Within a few hours the patient was extubated. He then seemed normal, except for slight disorientation and agitation. Twelve hours after cessation of sedation, the patient was normal. To clarify and confirm the diagnosis of an adverse reaction to fentanyl, we carried out a provocation test after obtaining full informed consent. A dose of 0.1 mg fentanyl intravenously was enough to induce agitation, generalised myoclonus, and paroxysmal dystonic movements and rigor that particularly affected the legs. No cognitive disturbances were apparent. The fentanyl dose was then increased to a total of 0.2 mg. At this point, a 6 mg dose of diazepam was given but did not improve the agitation of the patient. In fact the patient reported increased agitation. Administration of a morphine antagonist, naloxone (0.8 mg intravenously) dramatically improved his condition, completely normalising the myoclonus, rigor, and paroxysmal movements. No further improvement occurred on administration of the benzodiazepine antagonist flumazenil (0.25 mg intravenously). As the effect of the naloxone wore off, there was a