Deaths and disability from natalizumab are no longer tolerable: Yes

Pierre Duquette

Multiple sclerosis (MS) has an unpredictable course; while its course varies greatly from one individual to another, the overall life expectancy is 95% of normal. In the Vancouver cohort, secondary progression is attained 19 years after onset1 and the median time to Expanded Disability Status Scale (EDSS) 6.0 is 28 years.2 There is some evidence that the course of MS is not as aggressive as before.

Interferons (IFNs) and glatiramer acetate (GA) have been available for almost 20 years, with moderate efficacy, but low toxicity. A few cases of fulminant hepatic necrosis, necessitating a liver graft, have been reported in patients on IFNs; about 10% of patients on IFNs experience low and reversible increases of liver enzymes, or thyroid dysfunction. It has been reported that IFNs reduces mortality. No serious adverse effects and no mortality have been associated with GA.

Natalizumab (NTZ) is the first humanized monoclonal antibody used in MS. In 2011 a systematic review of trials evaluating NTZ for relapsing forms of MS3 showed that NTZ significantly reduced the risk of having a relapse (relative risk [RR] 0.57) and the risk of experiencing progression (RR 0.74). In these trials, 60% of NTZ-treated patients had no new MRI lesions. In addition, 64% of patients were ‘disease free’, but in other trials this percentage decreased to 37.8%. It is unknown if this level of efficacy will be retained over the long term.

NTZ was pulled from the market in 2005 after three cases of progressive multifocal leukoencephalitis (PML) had been reported. It was reintroduced in 2006, under a strict surveillance program. The manufacturer, Biogen-Idec, has been diligent in reporting new cases of PML. In the last (available at time of writing) report (February 2012): 95,300 MS patients had been exposed to NTZ, resulting in 207 PML cases and 44 (21%) deaths, with at least as many severely disabled. When 1,000,000 patients will have been exposed, we will number 2172 PML cases, 461 deaths and 461 severely disabled. These extremely serious adverse events are incurred for a disabling but not fatal disease, whose prognosis is obscure. Is this acceptable? Can we justify exposing patients to that degree of risk?

Three factors increasing the risk for PML have been identified: prior use of immunosuppression (IS), having received ≥24 infusions and a positive test for antibodies against the JC virus (JC Abs). A recent paper has detailed the risk of PML in NTZ-treated patients.4 The minimal risk of PML is 0.00006%, quite a low figure, but the maximal risk is 1.17%, not so low. Although the risk seems to plateau after three years of exposure, the number of patients at that level of risk is low, so that we cannot be reassured that the risk will not increase over time. The frequency of PML could be underestimated, given that reporting is on a voluntary basis. Will other opportunistic infections become manifest with time?

The gain of efficacy of NTZ over disease-modifying drugs (DMTs) is of the order of 2 or 3. The ‘gain’ in mortality/morbidity could be as high as 400. There is just no comparison. When considering cost-effectiveness, how much value is attributed to remaining alive, or free from severe drug-induced disability? The benefit for the drug company is obvious: at an annual cost of US$44,000 over 2 years for 100,000 patients, the gross income is US$8.8 billion.

The American Academy of Neurology 2008 guidelines recommend NTZ for the treatment of patients with relapsing–remitting MS who have failed other therapies because of continued disease activity, or medication intolerance, or who have a very aggressive initial disease course.5 In this perspective, prescribing NTZ for the sole reason of needle phobia seems unacceptable. Following these guidelines would decrease the number of patients at risk. In the global MS population, 56% have JC Abs but every year, 3–4% will convert from negative to positive JC Abs.6 What is the risk of PML in these seroconverted patients? Patients must be fully informed of the risks. NTZ does increase the possibility of remaining disease free, but disease free does not mean risk free. Should NTZ be used for short periods of time, i.e. 12–18 months, and then tapered gradually, while reinstituting standard disease-modifying treatments (DMTs)? If treatment is stopped before 24 months, is the risk averted? Will the disease revert to its baseline?
condition? Consideration was given to drug holidays in the hope of decreasing the risk of PML but, when attempted, disease activity rebounded in up to 80% of cases.\textsuperscript{7} In addition, the immune reconstitution inflammatory syndrome can supervene when NTZ is stopped.\textsuperscript{8} NTZ can be detectable in the blood up to 200 days after cessation of therapy.\textsuperscript{9} Stopping NTZ is then problematic. If there is no response to NTZ, which treatment can be used, knowing that IS increases the risk of PML? The use of NTZ may restrict access to other treatments.

It is often mentioned that patients are less risk averse than neurologists are, given that they expect to benefit from the drug. In addition, some patients insist on staying on treatment with NTZ, even as they have Abs against JC virus, on the basis that their previously active disease is now under control. This is debatable on an individual basis. Concern arises when we start adding numbers globally.

In conclusion, the availability of NTZ has resulted in a new wave of PML cases, with its incumbent risk of mortality and morbidity. These are entirely iatrogenic. A higher rate of PML with more prolonged use cannot be excluded. NTZ is not a cure for MS and, in the long run, all we might have achieved is to obtain a halt in the remitting phase of MS with little, if any, impact on its progressive phase. The cost in mortality/morbidity would then appear as prohibitive. We should consider that too intense an immunomodulation results in a too high degree of opportunistic infections, all the while preventing the reparative aspect of inflammation. We have to keep searching for better and safer therapeutic options.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest
The authors declare no conflicts of interest in preparing this article.

References