Estimating the PML risk on natalizumab: a simple approach

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Abstract

In this short note, we show how to quickly verify the correctness of the estimates of the PML risk on natalizumab established in [Borchardt 2015]. Our approach is simple and elementary in that it requires virtually no knowledge of either statistics or probability theory. For a Kaplan-Meier curve of the PML incidence may be found in [O'Connor et al 2014], based on postmarketing data as of early August 2013, and just using the information from that chart, it is possible to directly derive estimates of the risk of PML in JCV-seropositive natalizumab-treated patients according to prior or no prior immunosuppression. Actually, the resulting figures are almost identical to the ones in [Borchardt 2015], even though the latter were obtained in a very different fashion.

Results

The following shows Biogen's estimates [TY-PAN-0597(17) 2014] of the PML incidence among JCV-seropositive natalizumab-treated people against the respective estimates from this article:

constellation	Biogen	realistic
months 25–48, prior IS	11.2‰ (1 : 89)	19.3‰ (1 : 52)
months 25–48, no prior IS	5.3‰ (1 : 189)	7.4‰ (1 : 135)
months 49–72, no prior IS	6.1‰ (1 : 164)	10.8‰ (1 : 93)

Introduction

In [Borchardt 2015], we calculated the following estimates of the PML risk during natalizumab treatment, which are significantly higher than those from [Bloomgren et al 2012] as well as the ones stated in Biogen's quarterly PML update of December 2014 [TY-PAN-0597(17) 2014]:

constellation	PML risk estimate
months 25–48, prior IS	19.5‰ (1 : 51)
months 25–48, no prior IS	7.4‰ (1 : 135)
months 49–72, no prior IS	11.0‰ (1 : 91)

Table 1: Estimates of the incidence of natalizumab-associated PML from [Borchardt 2015].

However, the method by which these rates were deduced is a bit involved. In this article, we shall therefore demonstrate how to come by precise risk estimates using a rather different, and indeed considerably simpler, approach; the results will be more or less the same as the above ones.

For their review of Tysabri [EMA 2015], the EMA requested that Biogen furnish Kaplan-Meier curves of the PML incidence. Actually, just such a curve was once published using postmarketing data, namely as part of the supplementary material to [O'Connor et al 2014]. The graph that we will be interested in is Figure e-3; an approximate transcription looks like so:

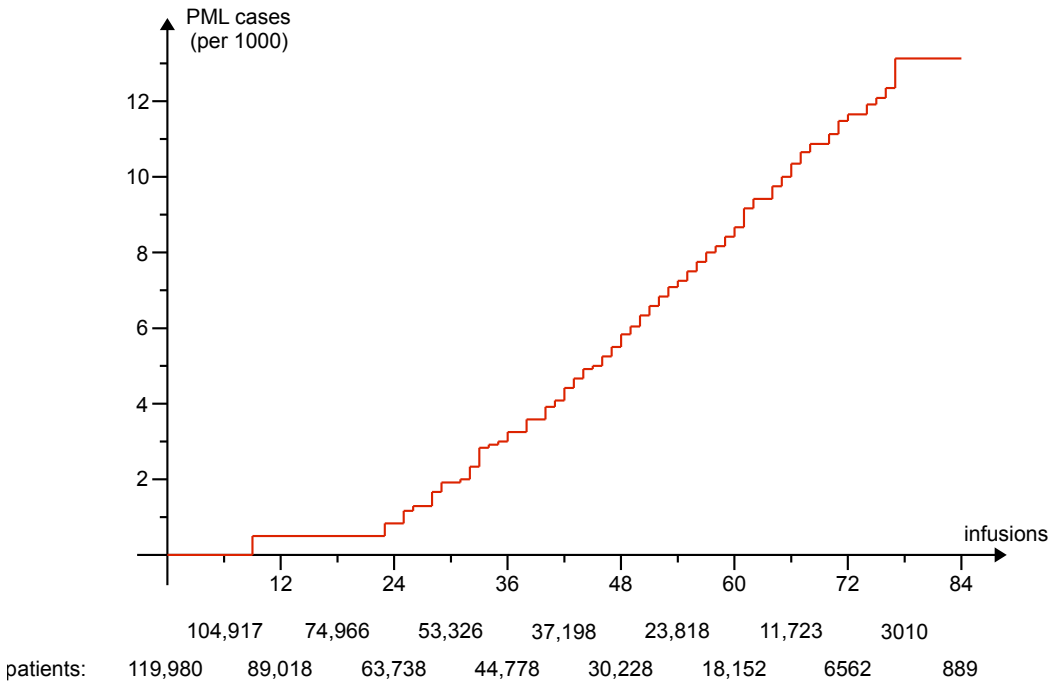

Figure 1: Kaplan-Meier curve of the postmarketing PML incidence in natalizumab-treated patients as of Aug. 2013, transcribed from [O'Connor et al 2014, Figure e-3].

Below we will explain why this diagram is essentially all we need in order to be able to check the findings from [Borchardt 2015].

Months 25–48

From Figure 1, simply by reading off, the PML incidence for the first 24 months (26 infusions) of natalizumab giving is around 1.3‰; for the first 48 months (52 infusions), it is 6.8‰. Therefore

the risk of getting PML in the course of months 25–48 (infusions 27–52) is about

$$6.8‰ - 1.3‰ = 5.5‰.$$

Actually, strictly speaking, that risk is really

$$\frac{6.8‰ - 1.3‰}{1 - 1.3‰} = 5.51‰, \tag{1}$$

because only those patients who did not already develop PML during the first 24 months should be included, obviously. Crucially, this 5.51‰ incidence concerns *everybody*, ie, it disregards both JCV status and pretherapies. Nevertheless, since the JCV-seroprevalence and the percentage of the previous immunosuppressant use are known, it is feasible to 'unwind' the overall estimate (1) and to hence easily determine the respective PML incidence among JCV-seropositive individuals with vs without prior immunosuppressive exposure. We will now describe how to accomplish this.

In [Borchardt 2015, §5], we showed that the 55% JCV-seroprevalence that Biogen base their risk assessments on is, with the second-generation ELISA, somewhat conservative an assumption; a truer proportion is 58.4%. Additionally considering that one in 86 natalizumab-associated PML cases in fact occurs in a JCV-negative person,[1] by (1), the incidence in JCV-positive people is

$$\frac{5.51‰ \times 85 \div 86}{58.4\%} = 9.33‰. \tag{2}$$

Now we merely have to separate out natalizumab users with past immunosuppression from those without pretreatment of this type, and we are finished. So suppose that p is the risk of PML for months 25–48 of a JCV-seropositive patient with no prior exposure to immunosuppressants, and pick λ such that λp equals the risk for the same constellation but with former immunosuppressive therapy. To realistically approximate λ, we shall rely on our own, earlier estimates (Table 1); thus

$$\lambda = \frac{\lambda p}{p} \approx \frac{19.5‰}{7.4‰} \approx 2.6.^{2} \tag{3}$$

Next, the previous usage of immunosuppressants among natalizumab-treated individuals is around 16% [Borchardt 2015, §5]. And that is indeed all the information we need—using (2), we have

$$16\% \times \lambda p + 84\% \times p = 9.33‰. \tag{4}$$

Plugging in the numerical value (3) for λ and solving for p, we finally get

$$p = \frac{9.33‰}{16\% \times 2.6 + 84\%} = \frac{9.33‰}{1.256} \approx 7.43‰, \tag{5}$$

[1] From [TY-PAN-0597(17) 2014, slide 23], as of 3rd December 2014, just three out of 258 natalizumab-treated PML patients (1 in 86) with known JCV serostatus were negative prior to diagnosis.

[2] Biogen's PML risk estimates would have yielded a factor of $(11.2‰ \div 5.3‰) \approx 2.1$.

and therefore

$$\lambda p = 2.6 \times 7.43‰ \approx 19.3‰. \tag{6}$$

Note that these last two PML incidence estimates—19.3‰ and 7.4‰ for people with vs without prior immunosuppressive exposure—are practically respectively exactly equal to the corresponding ones from Table 1 (19.5‰ and 7.4‰), despite the fact that, in contrast to [Borchardt 2015], we assumed no deriskification going on at all, ie, we pretended that there was no correlation between PML risk-factors and patients' dropout behaviour, which is certainly unrealistic. Hence, in truth, the quantities (5) and especially (6) are most likely a little greater still.

Months 49–72

When estimating the PML incidence during months 49–72 of natalizumab therapy, we *will* in fact take into account that risk-stratification has had some effect on peoples' treatment decisions (see [Borchardt 2015, §4] for statistically significant evidence about that). In detail, the meta-analysis carried out in [Borchardt 2015, §5] showed that roughly 60% and 30.4% of JCV-positive patients with respectively without former immunosuppression quit natalizumab sometime in the course of months 25–48 while the same happens with merely 12.3% of JCV-negative people. Consequently, in individuals with over four years' exposure, the JCV-seroprevalence is lower than on average, as is the past immunosuppressant usage. Precisely, on these assumptions, among natalizumab users with four years of treatment, just 50.9% are JCV-seropositive (vs 58.4% of all patients with MS), and only 9.9% (vs 16%) have had immunosuppressive pretherapy.

Importantly, these two rates were established as if PML risk-stratification had been performed routinely right from the market introduction of natalizumab, but of course, JCV serology testing did not actually become widely available until 2011. However, as of 6$^{\text{th}}$ August 2013—the cutoff for the collection of the data shown in Figure 1—fewer than one tenth of all natalizumab doses administered to people in either their fifth or sixth year of treatment fell into the pre-JCV-testing period. Nonetheless, so as not to overstate the risk, we will assume that the JCV-seroprevalence in postmarketing patients with 49 or more months of therapy for the dataset in question was not 50.9% but 51.7%,[3] and that the frequency of the previous use of immunosuppression was 10.5% instead of 9.9%.[4] For the same reason, we will further suppose that no deriskification beyond the fourth year took place.

The remaining piece of information required for the computation of the PML incidence as in the preceding section is how much higher the risk is in JCV-positive individuals with vs without

[3] $10\% \times 58.4\% + 90\% \times 50.9\% = 51.65\%$

[4] $10\% \times 16\% + 90\% \times 9.9\% = 10.51\%$.

previous immunosuppressant use. In the earlier notation, we need the approximate value of λ for months 49–72, cf (3). As we will justify below, the choice

$$\lambda = 2.2 \tag{7}$$

should be a realistic one, ie, for the treatment interval under consideration, we shall work on the premise that somebody with past immunosuppressive exposure has 2.2 times the odds of getting PML compared to a person who has never used such medication.

At last we are in a position to estimate the PML risk for months 49–72 (infusions 53–78) of natalizumab therapy in JCV-seropositive patients. Once more from Figure 1, upon inspection, the cumulative risk of developing PML at some point during the first 78 natalizumab infusions equals 13.1‰, and for the first 52 infusions, as observed already, the risk is 6.8‰. Hence the PML risk for infusions 53–78 is

$$\frac{13.1‰ - 6.8‰}{1 - 6.8‰} = 6.34‰.$$

However, this is again the average over *all* patients, regardless of JCV serostatus; the risk just in JCV-positive people is given by

$$\frac{6.34‰ \times 85 \div 86}{51.7\%} = 12.12‰. \tag{8}$$

Here, we use what we noted in the beginning of this section, namely, that merely about 51.7% of postmarketing patients with 53–78 infusions as of August 2013 were JCV-seropositive; as before, we also assume that one out of 86 PML cases occurs in a JCV-seronegative individual.

Finally, we need to disentangle the estimate (8) as we did for months 25–48, cf (4); if λp and p are the risks in patients with respectively without immunosuppressive pretherapy, then

$$10.5\% \times \lambda p + 89.5\% \times p = 12.12‰, \tag{9}$$

recalling that approximately 10.5% of JCV-seropositive patients had had prior immunosuppression with the dataset concerned. Substituting (7) into (9) and solving for p, we obtain

$$p = \frac{12.12‰}{10.5\% \times 2.2 + 89.5\%} = \frac{12.12‰}{1.126} \approx 10.76‰. \tag{10}$$

So the risk of PML during months 49–72 of natalizumab treatment in JCV-seropositive patients not having used immunosuppressive agents is about 10.8‰. We reiterate that this estimate was calculated as if there was no patient stratification in years five and six of therapy, ie, we supposed that during months 49–72, JCV-positive individuals stop natalizumab no more frequently than do JCV-negative ones. Given that this is surely not quite the case, the true value of p should be (at least) slightly bigger than the right-hand side of (10).

Lastly, we have to explain why we assumed that $\lambda = 2.2$, see (7), ie, why the PML incidence in the fifth and sixth years on natalizumab among JCV-seropositive people with previous exposure to immunosuppressants is around 2.2 times of what it is without pretreatment of this kind. From Table 1 in [Tysabri PI 2013], on the basis of postmarketing PML data as of 3rd September 2013, Biogen compute that in the United States, the former incidence is 9‰ while the latter is 7‰. As shown in [Borchardt 2015] though, these figures underestimate the reality because the drugmaker effectively calculates as if everybody who had started the fifth year of therapy had in fact finished six years, an assumption that is true for only a subset of patients. For example, with the (global) data from Figure 1—which incidentally had almost the same cutoff date as those used to assess the above-cited US risks—of the about 24,800 postmarketing patients with at least 53 infusions, merely 3010 individuals (12.1%) had in fact received 78 infusions. Therefore, a correction factor needs to be applied in order to obtain accurate PML incidence estimates.

Actually, as the relative risk of PML reaches a plateau before the end of the fourth treatment year, it follows—certainly on the assumption that any deriskification in the fifth and sixth years is similar in JCV-seropositive people with vs without previous immunosuppressive therapy—that the correction factor is independent of whether or not prior immunosuppression has taken place; call this constant ω. (As we will see directly, the numerical value of ω is unimportant since ω appears in both the numerator and the denominator of the ratio in question, so that the two occurrences of ω cancel each other out.)

One more aspect needs to be taken account of, namely, that the discontinuation rate during months 25–48 of therapy is greater in JCV-seropositive natalizumab users with past exposure to immunosuppression than among those without (approximately 60% vs 30.4%). Equivalently, the continuation rate in the former group is smaller compared to the latter (40% vs 69.6%). Putting together everything we just noted, we get

$$\begin{aligned} p &= \frac{\omega \times 7‰}{1 - 30.4\%}, \\ \lambda p &= \frac{\omega \times 9‰}{1 - 60\%}, \end{aligned}$$

and therefore

$$\lambda = \frac{\lambda p}{p} = \frac{\frac{\omega \times 9‰}{1-60\%}}{\frac{\omega \times 7‰}{1-30.4\%}} = \frac{9 \div 0.4}{7 \div 0.696} \approx 2.2,$$

as claimed.

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