Journal of NeuroVirology, 7: 323–328, 2001
 ISSN 1355-0284/01 $12.00+.00

Epidemiology Report

Epidemiology and prognosis of AIDS-associated progressive multifocal leukoencephalopathy in the HAART era

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Whereas most AIDS-related neurologic disorders have reduced incidence since HAART therapy was introduced, we find that the incidence of progressive multifocal leukoencephalopathy (PML) did not significantly differ between the pre-HAART and the HAART period (OR 0.78; 95% CI 0.41–1.50). These findings were confirmed by the preliminary results of the Italian Register Investigative Neuro AIDS (IRINA) Study, a prospective multicenter study started in January 2000, which showed that PML was the second most frequently diagnosed neurologic disorder after TE. A similar proportion of cases were found in HAART-na¨ve and HAART-experienced patients in our experience. PML was more common in the presence of HIV RNA >500 copies/ml. Most of the cases occurring in HAART-exposed patients developed within the first 6 months of therapy. As others have reported, we find a prolonged survival in PML subjects prescribed HAART (245 days in the group treated with HAART versus 66 days in the group not treated with HAART; *P* at log rank = 0.001). However despite the survival benefit, AIDS-associated PML still has a serious prognosis. In fact, PML had the lowest 1-year survival probability of any cerebral disorder in our study (*P* = 0.0005). Our findings also confirm that CSF JCV DNA burden at baseline is a useful prognostic indicator with a threshold of 4.7 $\log_{10}$ JCV copies/ml (*P* at log rank = 0.01) in our experience. CSF JCV DNA load at 4 weeks of follow-up and clearance of JCV-DNA from CSF are associated with a better neurologic outcome and a longer survival. *Journal of NeuroVirology* (2001) **7,** 323–328.

Keywords: PML; JCV; incidence; prevalence; prognosis; central nervous system; HIV; AIDS

Before the introduction of highly active antiretroviral therapy (HAART), progressive multifocal leukoencephalopathy (PML) was estimated to affect 1–4% of HIV-infected subjects (Berger *et al*, 1987) and was almost inevitably associated with a rapidly fatal outcome in the absence of an effective treatment option. It is well-known that in the era of HAART, dramatic declines in morbidity caused by some AIDS-associated opportunistic infections and tumors and in mortality were observed (Palella *et al*, 1998). We conducted several studies to assess temporal trends of AIDS-associated central nervous system (CNS) disorders, to identify clinical, neuroradiological, and virological prognostic factors, and to evaluate survival among HIV-infected patients with PML.

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Received 13 March 2001; revised 30 March 2001; accepted 20 April 2001.

Epidemiology

Since the widespread introduction of HAART for the treatment of HIV infection, a dramatic reduction in

the incidence of AIDS-related neurologic disorders has been documented (Brodt *et al*, 1997; Beck *et al*, 1999; d'Arminio *et al*, 2000; Sacktor *et al*, 2001). Nevertheless, the decrease in PML incidence has been less marked, with a rate of 0.14–0.3 per 100 person-years during the HAART period (Beck *et al*, 1999; Ledergerber *et al*, 1999; Sacktor *et al*, 2001).

The lesser extent of the impact of HAART on PML was confirmed in our experience when we compared the years since the introduction of HAART in Italy (1997–1998) with the pre-HAART era (1991–1996) for trends in the proportions of HIV-related focal brain lesion (FBL)-causing disorders (Ammassari *et al*, 2000). (At the Department of Infectious Diseases of the Catholic University, Rome, Italy, 281 consecutive patients with HIV infection, neurologic signs or symptoms, and at least 1 FBL on CT or MRI were observed between January 1, 1991 and December 3, 1998. Diagnostic criteria for PML were histologic proof on tissue specimens or positive JC virus (JCV) DNA on polymerase chain reaction (PCR) from cerebrospinal fluid (CSF) accompanied by a typical MRI pattern for PML). Of the 258 patients eligible for analysis, PML was diagnosed in 47 (18%). The other major diagnoses were toxoplasmic encephalitis (TE) in 94 cases (36.4%), primary nervous central system lymphoma (PCNSL) in 69 (26.7%), HIV encephalopathy in 13 (5.0%), cytomegalovirus encephalitis in 11 (4.2%), HSV encephalitis in 8 (3.1%), mycotic abscess in 7 (2.7%), and tuberculoma in 5 (1.9%). Our results showed a similar probability of PML in the pre-HAART and in the HAART period (OR 0.78; 95%CI 0.41–1.50), while a significant reduction in the risk of TE and of PCNSL were found. Moreover, on analysis of temporal trends, PML incidence remained stable over the HAART period, with a slightly increased risk for 1998 compared to 1996 (OR 2.00 for 1998; P for trend = 0.27).

Additional findings were obtained from the preliminary analysis of another study, which is the Italian Register Investigative NeuroAIDS (IRINA) Study (Antinori *et al*, 2001a). This is an ongoing prospective multicenter study designed to survey epidemiologic changes and natural history of AIDS-related neurologic disorders in the era of HAART. A secondary objective is to assess diagnostic criteria used in clinical centers based on available resources and to work out standardized guidelines. The study started in January 1, 2000, and involved 68 Italian AIDS clinical centers, which reported each consecutive patient presenting with an AIDS-related CNS disorder. Data regarding demographic and epidemiologic characteristics, history of HIV infection and anti-retroviral therapy, clinical and radiologic features, diagnostic criteria employed and availability of biologic samples were collected. During the first study year, a total of 311 cases were identified. The preliminary results of this study conducted during the HAART era show that PML was the second most frequent CNS disorder after TE. Furthermore, when comparing the proportions of cases among na¨ve and HAART-experienced patients, the risk of PML was not significantly different, especially within the first 6 months of treatment (Figure 1). Moreover, PML was more common in the presence of HIV RNA >500 copies/ml (82%) occurring at a median value of 4.99 $\log_{10}$ copies/ml (IQR 3.19–5.44). Median CD4 count was 63 cells/μl, with only 18% of cases presenting at values above

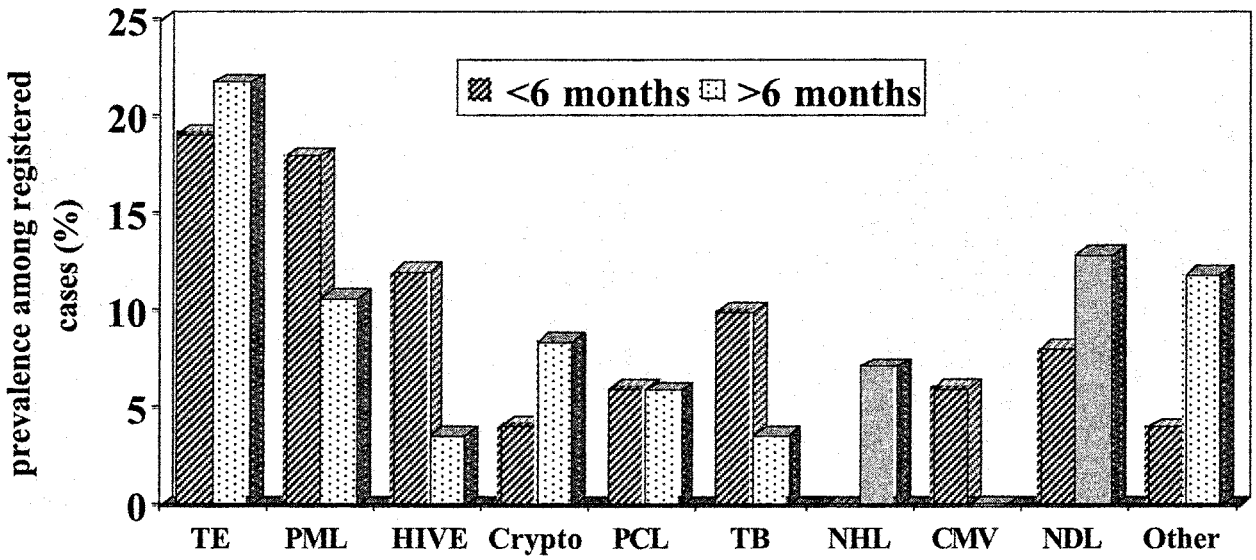

Figure 1 Proportions of different AIDS-associated central nervous system disorders according to time being treated with HAART (>6 months vs <6 months). (TE = toxoplasmic encephalitis; PML = progressive multifocal leukoencephalopathy; HIVE = HIV encephalopathy; Crypto = cerebral cryptococcosis; PCL = primary cerebral lymphoma; TB = cerebral tuberculosis; NHL = cerebral localization of systemic non-Hodgkin lymphoma; CMV = cytomegalovirus encephalitis; NDL = not determined leukoencephalopathy.)

200 cells/μl. In the same study, a total of 25 (8%) patients presented a picture of leukoencephalopathy that remained undiagnosed even after CSF investigation by multiple PCR. Sixty-eight percent of these subjects had HAART experience, with more than 6 months of treatment in 44% of cases. Median CD4 count at leukoencephalopathy diagnosis was 126 cells/μl (IQR 54–288) with 36% of cases occurring at values above 200 cells/μl. HIV RNA was undetectable in 21% of cases. Presence of focal signs was the most frequent clinical finding (68%). At neuroimaging, all patients showed white matter involvement with a focal/multifocal pattern in 76% of cases. Mass effect or contrast enhancement were generally absent. Hypointensity in T1-weighted and hyperintensity in T2-weighted images were found on MRI in 67% and 79%, respectively. Brain atrophy was observed in only 16% of patients.

Our findings are consistent with those of Ledergerber *et al* (Ledergerber *et al*, 1999), who documented that 75% of PML cases developing under HAART present during the first 3 months of therapy. Among the possible reasons for the lack of effect of HAART on occurrence of PML is evidence that PML can also develop in persons with relatively high CD4 cell count or suppressed viral replication (Berger *et al*, 1998; Gasnault *et al*, 1999; Tantisiriwat *et al*, 1999; Antinori *et al*, 2001a). In addition, it is well-known that PML, as other opportunistic infections, can be observed in patients in whom immune reconstitution is achieved by HAART (Mayo *et al*, 1998; Collazos *et al*, 1999). Especially during the first months of treatment, JCV-specific humoral and cellular immune defences might not completely be restored (Autran *et al*, 1997; Giudici *et al*, 2000). Finally, the CNS may be a virologically independent compartment relative to the plasma, resulting in some patients with poor HAART response only in the CNS (Ellis *et al*, 1997).

It is possible that undiagnosed white matter conditions are PML with a negative JCV DNA in CSF. This hypothesis is supported by the focal/multifocal pattern and the typical findings at MRI investigation, as well as by the observation that JCV DNA PCR sensitivity might be reduced in HAART-treated patients (Cinque *et al*, 1998). Other explanations for these undiagnosed leukoencephalopathies could be atypical focal HIV encephalopathy or other emerging AIDS-related CNS disorders.

Prognosis

Survival

In the pre-HAART era, AIDS-associated PML was considered an usually untreatable and rapidly fatal disease with a median survival of about 2.5–4 months after diagnosis (Berger *et al*, 1987; Fong *et al*, 1995). Several more recent studies (Clifford *et al*, 1999; Dworkin *et al*, 1999; Gasnault *et al*, 1999; Tassie *et al*, 1999) documented a prolonged survival and a reduced risk of mortality in subjects with PML taking HAART regimens that included protease inhibitors.

The strong benefit conferred by HAART in AIDS-associated PML was confirmed in our experience. In a multicenter study (De Luca *et al*, 2000) of 57 HIV-1-infected subjects with the diagnosis of PML, the median survival time in those treated with HAART, with or without cidofovir, was significantly longer than that observed in patients receiving cytarabine with or without a concomitant mono or dual antiretroviral therapy (245 days vs 66 days; P at log rank = 0.001). HAART was associated with longer survival even after exclusion of the 14 patients who were concomitantly treated with cidofovir (P at log rank = 0.02). The cumulative proportion of HAART-treated patients surviving more than one year was 0.46 compared to 0.04 found in patients treated without HAART. All patients who died despite HAART did so during the first months with a median time from diagnosis to death of 7 weeks (range, 1–35).

Despite the benefit in survival time with HAART, AIDS-associated PML still carries a severe prognosis. At the National Institute for Infectious Diseases, L. Spallanzani IRCCS, Rome, Italy, we performed a study on 195 HIV-1-infected subjects with CNS disorders observed in the era of HAART to evaluate long-term survival and to assess factor predictive of mortality (Antinori *et al*, 2001b). Preliminary results show that diagnosis of PML was the only disorder associated with a lower cumulative 1-year probability of survival when compared to all other CNS disorders ($P = 0.0005$).

Prognostic factors

A correlation between JCV DNA burden in CSF at PML diagnosis and survival time has been shown in several studies (Taoufik *et al*, 1998; Koralnik *et al*, 1999; Yiannoutsos *et al*, 1999). This finding was confirmed in our experience (De Luca *et al*, 2000). In particular, we identified a threshold of 4.7 $\log_{10}$ JCV copies/ml at baseline that was associated with longer survival (P at log rank = 0.01). When HAART-treated patients were considered alone, baseline CSF JCV DNA level below 4.7 $\log_{10}$ copies/ml showed a significantly lower risk of mortality on univariate (unadjusted HR 0.22; 95%CI 0.07–0.64) and multivariate analysis (adjusted HR 0.13; 95%CI 0.02–0.65). In a previous study (De Luca *et al*, 1999) we found that the CSF JCV DNA at 4 weeks was significantly higher among subjects who showed progression of PML (mean $\pm$ SD, 4.47 $\pm$ 0.76 $\log_{10}$ copies/ml) than among stable patients (mean $\pm$ SD, 3.47 $\pm$ 0.57 $\log_{10}$ copies/ml) ($P = 0.027$). Furthermore, clearance of JCV DNA from CSF is associated with a better neurologic outcome and a longer survival (Cinque *et al*, 1998; De Luca *et al*, 2000; Taoufik *et al*, 2000). At the Department of Infectious Diseases of the Catholic University, Rome, Italy, we conducted a retrospective study to establish the predictive

value of clinical and neuroradiological variables on PML survival (Giancola *et al*, 2000). Forty subjects with AIDS-associated PML who received HAART ($n = 17$) or cytarabine with or without anti-retroviral monotherapy ($n = 23$) were included in the study. Brain MRIs were examined in a blinded fashion by a neuroradiologist and a score was calculated based on the number and localization of areas involved. The results showed a median MRI score of 10 (range, 1–23) with a median number of 2 brain lesions involved (range, 1–11). On multivariate analysis by Cox regression model, MRI score was an independent predictor of longer survival ($P = 0.05$), as are treatment with HAART, higher Karnofsky performance status, and favourable neurological response at 2 months. Survival time of patients with PML does not seem to be influenced by clinical characteristics at presentation, with the exception of performance status. Severity of the baseline neurological picture did not correlate with clinical outcome at 4 weeks in the pre-HAART era (De Luca *et al*, 1999) or with survival in patients treated with HAART (De Luca *et al*, 2000). In contrast, worse baseline performance status was found predictive of a lower probability of survival (De Luca *et al*, 1999; Gasnault *et al*, 1999). During follow-up, the lack of neurological progression at 2 months from PML diagnosis was independently associated with longer survival (HR 0.05; 95%CI 0.00–0.48) (De Luca *et al*, 2000).

The relationship between HIV disease markers, such as CD4 cell count and HIV RNA load, and survival time has been extensively investigated. The risk for death among PML patients is significantly higher in subjects with lower CD4 cell count at diagnosis (Clifford *et al*, 1999; Fong *et al*, 1995; Gasnault *et al*, 1999; Tassie *et al*, 1999) and survival improves in the presence of an immunologic recovery under HAART (Dworkin *et al*, 1999). (Baseline plasma HIV RNA load was not predictive of subsequent survival in different patient populations (De Luca *et al*, 2000; Gasnault *et al*, 1999), whereas no consistent data is available on the value of HAART-induced viral load suppression during follow-up (Clifford *et al*, 1999; De Luca *et al*, 2000; Tantisiriwat *et al*, 1999).) Regarding the prognostic value of CSF HIV RNA level, we evaluated the effect of this variable on survival at baseline and follow-up and did not find a significant correlation (De Luca *et al*, 2000). Presence of an AIDS-defining event previous to PML diagnosis has not been found to be associated with a higher risk of death in several more recent studies (Dworkin *et al*, 1999; Gasnault *et al*, 1999; Tassie *et al*, 1999: De Luca *et al*, 2000).

Among general characteristics of patients, older age was found by some authors to relate to shorter survival (Gasnault *et al*, 1999), whereas gender and HIV transmission modality were consistently not associated with a worse prognosis.

In conclusion, in the era of HAART, PML remains a relevant AIDS-associated CNS disorder, representing the second most frequent diagnosis. Patients during the first months of treatment carry the highest risk, especially if HIV replication is not adequately suppressed. Nevertheless, the widespread use of HAART significantly improved survival time, although prognosis of HIV-infected patients with PML is still severe compared to that of subjects with other AIDS-related CNS disorders. Future research efforts should focus primarily on the relationship between PML, HIV, and HAART.

Acknowledgements

The authors thank the Scientific Committee of Italian Register Investigative Neuro AIDS (IRINA Study) and the participating clinical centers for allowing presentation of preliminary data. Most especially thanks to Paola Cinque (HSR, San Raffaele Hospital, Milan) for her role in the IRINA Project and for helpful comments. This work was supported by Istituto Superiore di Sanità, Italy, II e III Programma Nazionale di Ricerca sull'AIDS and by Ricerca Corrente e Finalizzata degli IRCCS, Ministero della Sanità, Italy.

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