Sir, Survival analyses are frequently used in the clinical literature. Discussions on their limitations should be useful. An example is that none of the large natural history databases (Weinshenker et al., 1989; Runmarker and Andersen, 1993; Kantarci et al., 1998; Confavreux et al., 2003) allow for prediction from the first bout, as a possible second (diagnostic) event is a precondition for the validity of these databases. The recent paper by Scalfari et al. (2010) has a dual result, the finding of a moderate predictive effect of a high attack frequency during Years 1–2 and the absence of relationship between the total number of attacks and time to secondary progression (Fig. 1D). However, there is no point in time that separates the predictors from the outcome in this analysis, so it is impossible to select an unobjectionable predictive variable from these data. An additional analysis was performed, reported in the ‘Discussion’ section of the Scalfari et al. (2010) paper, where no correlation for each 2-year block from Year 3 on could be found. However, with a higher number of attacks expected in the early phase and a higher number of years available for analysis (until the onset of secondary progression), the first episode has a priori a higher chance to show a significant correlation with the outcome variable. Therefore, it is difficult to pinpoint a limit for the predictive effect. The result that a longer time to endpoint (Disability Status Scale (DSS) 6) allows for more attacks before the endpoint (lower part of Table 3) is trivial and does in no way exclude specific predictors, such as timing and character of the relapses.

There is a related problem with the calculation of the prognostic effect of the first inter-attack interval (Table 8): the time to endpoint will a priori be longer with long inter-attack intervals, as the endpoint is not allowed to occur within these intervals.

The predictive power of early attack frequency has been examined in several studies. We found no predictive power of the early relapse frequency in the first 5-year period as a continuous variable (Runmarker and Andersen, 1993), although we later, after reorganizing the database to utilize prediction from the onset bout, found a negative prognostic effect of a small subgroup with high attack frequency (Eriksson et al., 1993). The result of the Scalfari et al. (2010) study is very similar in this aspect. We, as well as other groups, found that other predictors were more important, including remission from the onset attack, afferent course and monofocal symptomatology. These characteristics were not included in the Scalfari et al. (2010) study. However, based on the London Ontario database, Kremenchutzky et al. (2006) found that polyfocal symptoms were associated with a negative prognosis. In this material, but examined only in their single attack progressive subsample, no effect of remission of the onset bout was found. In our hands, the prognostic effect of the clinical characteristics’ remission, afferent course and polyfocality was as least as strong from a later bout (last bout in the first 5-year period) as from the onset bout (Runmarker and Andersen, 1993; Eriksson et al., 2003).

These predictors suggest that the components typical of a serious, progressive course (motor symptomatology, irreversibility) are already discernible, although intermittently, in the relapsing–remitting phase. We agree with Professor Ebers that factors driving the accumulation of severe disability are already active during the early phases of the disease, which may represent a window of opportunity for therapy. The argument that the effect of relapses in Years 1–2 on the risk (hazard ratio, Table 6) to reach DSS 6 from onset of secondary progression is driven by early deficit accumulation rather than early relapses deserves a formal analysis. The significant prognostic effect of relapse frequency in Years 1–2 (Scalfari et al., 2010) on the slope of secondary progression should not be
immediately disregarded. It may indicate a weak common (possibly inflammatory) component between the relapsing–remitting and the secondary progressive course.

Wallerian degeneration may be important in some situations (Evangelou et al., 2000). However, we found evidence supporting the notion that axonal degeneration occurs early in the course. Analysis of the levels of neurofilament in the CSF showed that increased level of neurofilament light is a general feature of multiple sclerosis, indicating continuous axonal damage during the entire course of the disease (Malmeström et al., 2003). Insidious loss of channels in the optic tract was found in almost all patients with multiple sclerosis at their first (non-optic) bout (Lycke et al., 2001). Importantly, if insidious neurodegeneration was triggered by inflammation, the triggering events were probably initiated many years before the first neurological manifestation.

The large re-evaluated London Ontario cohort of course has a potential far beyond the present partly negative findings. Improved methods to integrate and measure the effect of therapy against the natural history background are expected. Statistical methods capable of detecting prognostic effects changing (decreasing) with time could be used. The occurrence of independent predictors for the secondary progressive course may depend on genetic factors, of which only a minor fraction of those related to multiple sclerosis susceptibility have been tested for association with type of course (Ramagopalan et al., 2008). The present discussion on the details of the Kaplan–Meier analysis should be seen against the background that survival analyses will continue to be essential for these developments.

References


