Teaching Course 11

Therapeutic strategy in MS: How to choose the appropriate disease modifying treatment - Level 3

When and how to escalate MS treatment?

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1. Starting treatment: when and which

The modern era of MS treatment began after 1993, with the approval of three formulations of IFN-β and glatiramer acetate. A second important milestone in MS therapeutic development arrived with the approvals of natalizumab in late 2003. The third stage of MS therapeutic development came with the introduction of three oral immunomodulatory medications (fingolimod in 2009, teriflunomide and dimethyl fumarate in 2014). Finally more recently, new biologics (alemtuzumab (a CD52 antibody), daclizumab (a CD25 antibody) and ocrelizumab (CD20 antibodies) (Ransohoff, Hafler et al. 2015) have been approved.

With the progress of MS therapeutics, we have learned that the natural history of MS can be modified by treatment and that beginning treatment early produces better medium-term outcomes. A recent meta-analysis, has determined that in RRMS, higher treatment effects are associated with earlier (lower age and EDSS) and more active (higher gadolinium activity) disease (Signori, Schiavetti et al. 2015). Today, there is no clear biomarker that can predict response to therapy; therefore clinical judgement is still crucial in choosing therapy. With the arrival of more efficacious drugs, we are leaving behind the notion that all patients, regardless of their clinical state, should fail IFNB or glatiramer acetate before receiving a second-line treatment. For example female patients, wishing to have children, who have mild disease, it is reasonable to treat them with IFN-β or glatiramer acetate because of the safety profile in pregnant women (Thiel, Langer-Gould et al. 2016) (Herbstritt, Langer-Gould et al. 2016). By contrast, patients with substantial MRI lesions and brainstem or spinal cord disease who have had multiple exacerbations and have accumulated disability should probably be treated with the more-
efficacious therapies from the onset (Ransohoff, Hafler et al. 2015). The increasing complexity of MS treatments makes a compelling argument for patients to be followed at comprehensive MS centres with expertise in the use of immunotherapies (Ransohoff, Hafler et al. 2015).

2. When to escalate

Although data from large cohorts treated in real settings may present some bias (lack of randomization, heterogeneity in clinical care, and regression to the mean among others) and though observational studies cannot distinguish prognostic factors from treatment effect, they help to identify predictors of treatment response and to accrue information on the safety and efficacy of treatments in patients with other comorbidities (Sormani and Bruzzi 2015) (Marrie, Miller et al. 2016). In relapsing patients, the presence of clinical or MRI activity despite treatment with disease modifying drugs (DMD) is a relevant predictor of marked long-term disability (Rio, Nos et al. 2006) (Rudick, Lee et al. 2004, Rio, Comabella et al. 2009), (Bermel, You et al. 2013), (Jokubaitis, Spelman et al. 2016). Disability progression remains difficult to treat. It is worth hoping that the present therapeutic armamentarium will make a decisive difference in the occurrence or severity of progressive MS. In any scenario, progressive MS is the next frontline for MS research.

2.1 The role of clinical activity in predicting treatment response

The pivotal trial of IFNβ-1a IM demonstrated that patients with at least two relapses during the first two years of therapy had a higher risk of being in the worst EDSS quartile at 15 years (OR 4.44, CI 1.43-13.85, p<0.01) (Bermel, You et al. 2013). Interestingly, the impact of having two relapses in patients treated with placebo was not associated with this bad
outcome (Bermel, You et al. 2013). Similarly, another long term study of patients included in the pivotal trial of IFNβ-1b showed that changes in EDSS (p<0.0001) and relapse rate (p<0.025) during the study (0-2 years) were associated with a higher risk of reaching an EDSS score of 6.0 or transitioning to SPMS after 16 years (Goodin, Traboulsee et al. 2012). Similarly, in a cohort of patients who began therapy with IFNβ in our center in Barcelona, between 1995 and 2001, we also observed that the presence of relapses or EDSS worsening during the first 2 years of therapy had a very negative impact on the risk of developing SPMS, attaining an EDSS score of 7.5 or exhibiting an increase of at least 5 EDSS steps after 12 years of follow up (Rio et al., in press). However, it is important to note that the presence of an isolated relapse without changes in EDSS during the first two years of treatment did not significantly increased the risk of developing marked long-term disability (Rio et al., in press). Overall, the clinical activity measures at 2 years had good or moderate specificities and moderate or low sensitivities (Rio et al., in press). Other recent studies have also confirmed that clinical activity defined as an EDSS change or relapses during the first years of IFN treatment has a very negative impact in long-term prognosis (Rotstein, Healy et al. 2015), (Jokubaitis, Spelman et al. 2016).

2.2 The role of clinical and or MRI activity in predicting treatment response

MRI activity during the first months of IFN beta has also been correlated with a worse clinical outcome (Rio, Rovira et al. 2008, Dobson, Rudick et al. 2014, Prosperini, Mancinelli et al. 2014, Sormani, Gasperini et al. 2016). Many studies have assessed the role of clinical (relapses and disability progression) and/or MRI activity (defined as either new gadolinium enhancing lesions and/or new/enlarging T2-lesions compared
to baseline MRI scans) to define responder or non-responders to DMD (Rio, Rovira et al. 2008, Rio, Comabella et al. 2009) (Rio et al., in press; Prosperini, Mancinelli et al. 2014) (Sormani, Rio et al. 2013) (Dobson, Rudick et al. 2014) (Sormani, Gasperini et al. 2016). The different criteria or scores proposed to identify patients with suboptimal treatment response highlight the controversy on what degree of clinical or MRI activity should be accepted before defining a patient as non-responder to a therapy and therefore switching to another one.

With increasingly effective therapies “No evidence of disease activity” (NEDA) has gathered increasing consideration as a treatment goal. NEDA is a composite that advocates for the “zero tolerance concept” entailing for the absence of relapses, no sustained EDSS progression, and no new or enlarging T2 or T1 gadolinium-enhancing lesions on annual MRI. The definition of NEDA is recently evolving to include brain atrophy (Bevan and Cree 2014) (Kappos, De Stefano et al. 2016) as a meta-analysis demonstrates that both focal T2-lesion load over 2-years, and whole brain volume loss in year two, explained 75% of the variance of disability progression over 2 years on DMT, which was better than either metric alone (Sormani, Arnold et al. 2014). Other metrics such as patient-related outcome measures or fluid biomarkers, for example cerebrospinal fluid neurofilament levels could also be incorporated to the NEDA definition in the future (Stangel, Penner et al. 2015); (Kuhle, Disanto et al. 2015). However, the persistence of NEDA over time and its accuracy for predicting long-term prognosis is controversial (Rotstein, Healy et al. 2015).

The problem is to define what degree of early disease activity is associated with a poor long-term prognosis. Confounding factors such as
the timing of the reference scan in relation to treatment initiation, and 
the on-going disease activity before the drug becomes effective, together 
with insufficient repositioning and interobserver variability may explain 
these conflicting results (Erbayat Altay, Fisher et al. 2013) (Wattjes, 
Rovira et al. 2015). What emerges from the great majority of studies is 
that the combination of clinical relapses with MRI activity appears as the 
best predictor of short-term disease progression, whereas minimal MRI 
activity alone is controversial. The tolerance of some degree of activity 
(MEDA: minimal degree of disease activity) may be more realistic in real 
word settings. Another important weakness when evaluating tools for 
establishing treatment response is that the great majority of studies are 
based in patients under IFN treatment, with limited data in cohorts of 
patients treated with other DMDs collected from clinical practice (Rio et 
al., in press; (Boster, Ford et al. 2015). Moreover, the indication for 
changing treatment when using induction-therapy may probably be 
different to that of maintenance-treatment (Giovannoni, Turner et al. 
2015). For many treatments (IFN, cop, oral licenced drugs), early disease 
activity can be understood as a sub-optimal or non-response, however 
disease activity on an induction therapy, such as alemtuzumab, can be 
contemplated as an indication to retreat the patient (Giovannoni, Turner 
et al. 2015). Real-world data with long-term follow-up are needed for 
each therapy. Tools to better predict response to treatment even before 
starting a drug would be of more help to choose the right drug for the 
right patient, to prevent side effects and to achieve cost-effectiveness for 
our treatments.
2. How to escalate:

Evidence from randomized control trials and real-world observational studies suggests that escalation to second-line treatments (natalizumab, fingolimod, alemtuzumab, ocrelizumab) after treatment failure of first-line therapies is usually associated with a better control of inflammatory activity than switching between first line treatments (Trojano, Tintore et al. 2017) (Khatri, Barkhof et al. 2011) (Coles, Twyman et al. 2012) (Spelman, Kalincik et al. 2015) (Spelman, Mekhail et al. 2016) (He, Spelman et al. 2015) (Kalincik, Horakova et al. 2015) (Baroncini, Ghezzi et al. 2016) (Barbin, Rousseau et al. 2016, Koch-Henriksen, Magyari et al. 2017); Observational studies have also compared the benefits of escalation to natalizumab or fingolimod (Trojano, Tintore et al. 2017) (Kalincik, Horakova et al. 2015), (Barbin, Rousseau et al. 2016, Baroncini, Ghezzi et al. 2016). Escalation to natalizumab showed a lower relapse rate and a higher probability of disability regression than did escalation to fingolimod after propensity score matching (Kalincik, Horakova et al. 2015) Differences between natalizumab and fingolimod were more apparent in patients with highly active disease. Opposite to these studies, a study from the Danish MS Treatment Register found no difference between the natalizumab and fingolimod after a propensity score matching by baseline covariates (Koch-Henriksen, Magyari et al. 2017).

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Dr. Mar Tintoré received speaking honoraria and travel expenses for scientific meetings in the past with Amirall, Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Roche and Teva.
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