Highlights dal 34° Congresso ECTRIMS

Berlino, 10-12 ottobre 2018

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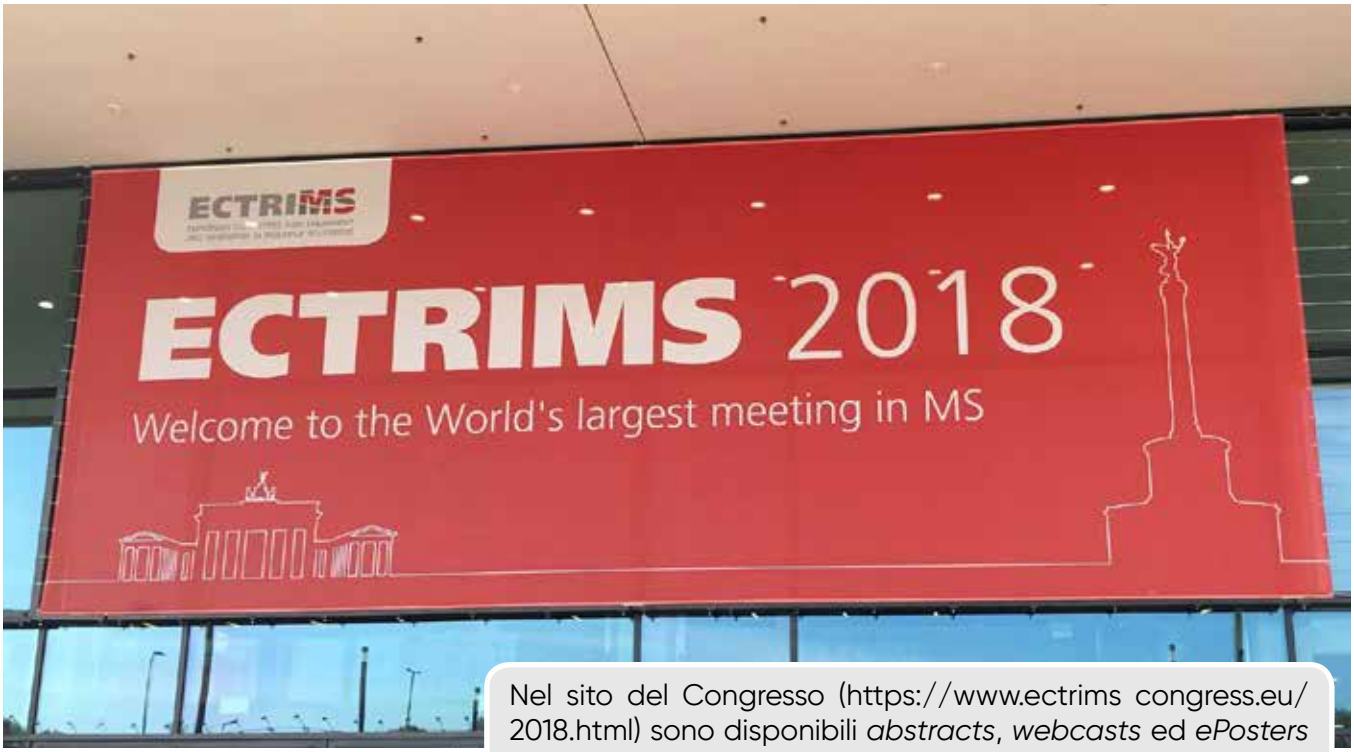
Quasi 10mila professionisti da oltre 100 Paesi. Queste, in sintesi, le cifre del rinnovato successo del Congresso dell'*European Committee for Treatment and Research in Multiple Sclerosis* (ECTRIMS) svoltosi quest'anno a Berlino. Ricercatori, clinici e vari *stakeholders* hanno condiviso esperienze e novità in tutte le aree della sclerosi multipla (SM): dalla genetica all'anatomo-patologia, dall'epidemiologia all'immunologia e, soprattutto, alla terapia.

Aperto, in sessione plenaria, da un'interessante lettura magistrale del Prof. Alastair Compston (Università di Cambridge, UK) sulla storia e il futuro della SM (*Multiple sclerosis in the digital age: 'seeing through a glass darkly*), il Congresso ha dato ampio spazio al tumultuoso sviluppo di informatica e bioingegneria, con interessanti sessioni su analisi multiomiche, processazione dei *big data*, elaborazione di algoritmi predittivi diagnostico-terapeutici, *imaging* molecolare, robotica e automazione in medicina. Prima di una rapida rassegna di alcune presentazioni di particolare interesse per il loro impatto clinico, meritano una segnalazione due importanti *highlights* emersi in ambito congressuale, ovvero:

- i progressi nell'individuazione di validi biomarcatori prognostici, con *focus* particolare sui neurofilamenti leggeri (NFL) di cui si è discusso tra l'altro in due Simposi, organizzati con il supporto non condizionante di Biogen *(Data, Analysis, Technology, Application - De-*



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velopments on the frontiers of MS) e di Novartis *(Committing to patients, impacting individuals: towards an individualised approach for patients with MS)*, e in una Sessione Scientifica *(Predicting the course of newly diagnosed patients: insights from cohorts)*, dove se ne è ipotizzata una prossima implementazione nella pratica clinica per la fenotipizzazione del paziente e il monitoraggio della risposta terapeutica. Gli NFL sono in effetti considerati espressione diretta di danno assonale infiammatorio acuto e precoce ed il loro incremento nel liquor/siero è correlato ad *outcomes* di infiammazione (lesioni captanti gadolinio all'*imaging* di risonanza magnetica - MRI) ed appare predittivo di più rapida conversione da sindrome clinicamente isolata (CIS) a SM recidivante-remittente conclamata (SM-RR) e di disabilità a lungo termine;

- l'importanza del coinvolgimento attivo della persona-paziente nella gestione della malattia, della promozione dei suoi diritti e dell'attenzione da riservare ai PRO (*Patient Reported Outcomes*, esiti riferiti dal paziente) e ai dati del mondo reale (RWD, *Real Word Data*) nella valutazione dell'efficacia di ogni intervento terapeutico.

Si segnala, a tal proposito, il sempre affollato stand dell'*European Multiple Sclerosis Platform - The voice of people with MS in Europe* (www.emsp.org), con aggiornamenti sullo sviluppo del Progetto *Multiple Sclerosis Data Alliance* (MSDA), in collaborazione con l'Università di Gottingen (Germania) e il cui programmatico claim è: *"better data for better decision making, a multi-stakeholder approach"*.

Cladribina. Nuove conferme di efficacia e sicurezza

Nuove analisi dei *trials* registrativi confermano l'efficacia nella *real life (effectiveness)* di cladribina nel ridurre le recidive e la progressione della disabilità nella SM recidivante-remittente (SM-RR). Cladribina appare efficace in pazienti di differente età e differente attività di malattia. In particolare, analisi *post-hoc* dello studio CLARITY[1] e della sua fase di estensione a 4 anni (CLARITY EXT) hanno dimostrato che cladribina (allo schema posologico approvato, ovvero massimo 20 giorni di terapia orale nei primi due anni)[2]:

- riduce significativamente a 2 anni (settimana 96) la frequenza di recidive, incluse quelle gravi. La riduzione del rischio (rispetto al placebo) è infatti del 63% per le recidive che richiedono ospedalizzazione e del 62% per quelle da trattare con steroidi (Poster P549);
- ha efficacia duratura (Poster P894), con stato NEDA-3 (*No Evidence of Disease Activity* per assenza di recidive, assenza di progressione della disabilità a 6 mesi valutata con EDSS, assenza di lesioni T1 gadolinio-positive e T2 attive all'*imaging* di risonanza magnetica) che persiste nel tempo anche nei pazienti randomizzati a placebo nella fase di estensione, in percentuali (46% a 4 anni, 35% a 5 anni dall'arruolamento iniziale) non significativamente differenti da quelle osservate nel braccio sottoposto ad un secondo ciclo di cladribina (48% a 4 e 5 anni).

POSTER P549

Schippling S., et al. CLARITY: an analysis of severity and frequency of relapses in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets or placebo.

Introduction: *In the CLARITY study, treatment with Cladribine Tablets 3.5 mg/kg (CT3.5) showed strong efficacy vs placebo (PBO) over 2 years in patients with relapsing multiple sclerosis (MS).*

Objective: *The effect of CT3.5 on the rate and severity of relapses (using hospitalisation and steroid use as proxy indicators), and the effect of adjusting for covariates was evaluated in post hoc analyses.*

Methods: *Qualifying relapse was defined by Kurtzke Functional Score status and specified clinical parameters. Qualifying relapse relative risk (RR) was estimated for patients treated with CT3.5 (N=433) and PBO (N=437) at Weeks 24, 48 and 96 by Poisson regression with treatment and various alternating covariates (gender, age, age at time of diagnosis, disease duration, and pre-treatment) as main effects and by adding treatment by covariate interaction effects. All relapses were also analysed; analyses were post hoc and exploratory.*

Results: *Risk of qualifying relapse was significantly lower for CT3.5 vs PBO at Weeks 24, 48 (both p< 0.001) and Week 96 (Week 96: RR 0.42 [95% confidence interval (CI) 0.34, 0.53]; p< .0001). RR of all relapses (Week 96; CT3.5 vs PBO) was 0.43 [95%CI 0.37, 0.51]; p< .0001. Annualised relapse rates for PBO and CT3.5 were 0.35 and 0.15, (qualifying) and 0.63 and 0.27 (all relapses), respectively. Compared to PBO, the CT3.5 group had a significantly reduced risk of qualifying relapses leading to hospitalisation at all timepoints (Week 96 RR 0.41 [95%CI 0.29, 0.57]; p< .0001) and qualifying relapses leading to steroid treatment (Week 96 RR 0.41 [95%CI 0.32, 0.53]; p< .0001). Risk reduction of all relapses for hospitalisation and steroid use were 63% and 62%, respectively (Week 96). Both age at time of diagnosis (p=0.0011) and prior use of disease modifying drugs (p=0.0002) had a significant effect on qualifying relapse rate by Week 96 when added separately to the model. Gender had a marginal effect (p=0.0783) while disease duration had no effect (p=0.8770). None of the covariates influenced the RR of qualifying relapse for CT3.5 vs PBO at Week 96.*

Conclusions: *The RR of qualifying relapse (and all relapses) was consistently and significantly lower in the CT3.5 group, vs. PBO, for every timepoint (Weeks 24, 48 and 96), including severe relapses requiring hospitalisation or steroid treatment. After adjusting for covariates, the treatment benefit of CT3.5 vs PBO was not diminished by any of these model adjustments.*

[1] *Lo studio CLARITY (Cladribine Tablets Treating MS Orally) e la sua fase di estensione (CLARITY extension) fanno parte del programma di sviluppo del farmaco che include anche gli studi ORACLE-MS (Oral Cladribine in Early MS) e ONWARD (Oral Cladribine Added ON.*

[2] *La dose raccomandata cumulativa di cladribina è di 3,5 mg/kg di peso corporeo in 2 anni, somministrata come 1 ciclo di trattamento da 1,75 mg/kg per anno. Ogni ciclo di trattamento consiste di 2 settimane di trattamento, una all'inizio del primo mese e una all'inizio del secondo mese dell'anno di trattamento corrispondente. Ogni settimana di trattamento consiste di 4 o 5 giorni in cui il paziente assume 10 mg o 20 mg (una o due compresse) come singola dose giornaliera, in base al peso corporeo.*

POSTER P894

Giovannoni G, et al. Durability of NEDA-3 status in patients with relapsing multiple sclerosis receiving cladribine tablets: CLARITY extension.

Introduction: *In the CLARITY study, Cladribine Tablets 3.5 mg/kg (CT3.5) showed strong efficacy vs placebo (PBO) over 2 years in patients with relapsing multiple sclerosis (RMS). No Evidence of Disease Activity-3 (NEDA-3) status was achieved in significantly more patients receiving CT3.5 than those receiving PBO (47% and 17%, respectively p< 0.0001). Efficacy in patients receiving CT3.5 in CLARITY was maintained in Years 3 and 4 when patients were randomised to PBO in CLARITY Ext after a variable bridging interval of up to 116 weeks duration when patients were not treated with Cladribine Tablets.*

Objective: *Post hoc analysis to determine NEDA-3 status in patients who received CT3.5 in CLARITY and who were then treated with PBO (CP3.5) or CT3.5 (CC7) in CLARITY Ext.*

Methods: *Patients were retrospectively analysed for NEDA-3 status (patients with no relapse, no 6-month Expanded Disability Status Scale (EDSS) progression and no T1 gadolinium-enhancing or active T2 lesions) in the first year of CLARITY Ext for the CP3.5 and CC7 groups; N=98 and N=186, respectively. Variable bridging interval from the core and Ext studies was used as a proxy to determine NEDA in a 12-month observation up to the end of Year 4 (Y4, bridging ≤43 weeks; CP3.5 group; N=54, CC7 group; N=98 with confirmed NEDA status) or up to the end of Year 5 (Y5, bridging >43 weeks; CP3.5 group; N=40, CC7 group; N=77 with confirmed NEDA status). Differences in NEDA-3 in the CP3.5 and CC7 group were analysed by logistic regression with duration of study bridging included as a fixed effect.*

Results: *In 12 months up to the end of Year 4, annual NEDA-3 was achieved in 46% (25/54) of patients in the CP3.5 group and 48% (47/98) in the CC7 group. Up to the end of Years 5 after commencing CLARITY, annual NEDA-3 was observed in 35% (14/40) of the CP3.5 group and 48% (37/77) of the CC7 group. Adjusting for the length of the bridging interval, there was no significant difference between annual NEDA-3 in the CP3.5 (41.5%, 95% CI 32.4-60.0%) and CC7 (48.0%, 95% CI 40.2-64.4%) groups p=0.31). The duration of bridging interval was not a significant variable (p=0.38). Similar patterns were observed when proportions of patients' annual relapse-free and annual 6-month EDSS progression free were examined.*

Conclusions: *In this post hoc analysis, following treatment with CT3.5 in Years 1 and 2, annual NEDA-3 status was sustained in patients treated with either CT3.5 or PBO in CLARITY Ext up to the end of Year 5.*

In altri termini, l'efficacia prolungata di cladribina è verosimilmente espressione del suo peculiare meccanismo di azione, in grado di indurre un *reset* "stabile" del sistema immunitario ad uno stato "fisiologico" di *non-self* reattività, *reset* che persiste appunto anche dopo la normalizzazione della conta linfocitaria. Inoltre, l'analisi per sottopopolazioni degli studi CLARITY/CLARITY EXT conferma la sostenibilità a lungo termine dell'effetto clinico del farmaco anche in pazienti ad elevata attività di malattia (HAD - *high disease activity*), definita sulla base di storia clinica di recidive, pregressa terapia e *imaging* di risonanza magnetica. Nei pazienti con HAD è stato riportato un tasso annualizzato di recidive (ARR) pari a 0,15, identico a quello della coorte con più bassa attività di malattia (Poster P564).

POSTER P564

Vermersch P, et al. Sustained efficacy in relapsing remitting multiple sclerosis following switch to placebo treatment from Cladribine Tablets in patients with high disease activity at baseline.

Introduction: *In CLARITY, Cladribine Tablets 3.5 mg/kg (CT3.5) showed strong efficacy vs placebo (PBO) over 2 years in patients with relapsing multiple sclerosis (RMS); efficacy was sustained in Years 3 and 4 without further treatment (CLARITY Ext). In CLARITY, patients with high disease activity (HDA) showed clinical and magnetic resonance imaging (MRI) responses to CT3.5 that were better than, or comparable to, those seen in the overall CLARITY population.*

Objectives: *Post hoc analysis to determine if the efficacy in patients with HDA treated with CT3.5 in CLARITY (Years 1 and 2) was sustained for the long term in patients receiving PBO in CLARITY Ext (Years 3 and 4).*

Methods: *This analysis used 2 sets of HDA criteria based on relapse history, prior treatment, and MRI characteristics: 1. High relapse activity (HRA), defined as ≥2 relapses during the year before study entry whether on disease modifying drug (DMD) treatment or not; 2. HRA plus disease activity on treatment (DAT), defined as ≥1 relapse during the year before study entry while on therapy with other DMDs AND ≥1 T1 gadolinium-enhancing (Gd+) or ≥9 T2 lesions. Clinical and MRI outcomes were analysed for patients (N=806) randomised to CLARITY Ext who fulfilled HRA and HRA+DAT cri-*

teria at CLARITY baseline and who received CT3.5 in CLARITY and PBO in CLARITY Ext.

Results: *The annualised relapse rate (ARR) for qualifying relapses in CLARITY Ext for the population who switched to placebo in Ext from CT3.5 in CLARITY (N=98) was 0.15 (95% confidence interval [CI]; 0.11, 0.21). ARRs for HRA (N=29) and non-HRA (N=69) were 0.15 (95%CI; 0.08, 0.28) and 0.15 (95%CI; 0.10, 0.22), respectively. For HRA+DAT (N=31) and non-HRA+DAT (N=67), ARRs were 0.14 (95%CI; 0.08, 0.26) and 0.15 (95%CI; 0.10, 0.22). The ARRs in this analysis were similar to those seen for the HDA subgroups in CLARITY. In this study, fewer patients in the HDA subgroups had confirmed 3-month Expanded Disability Status Scale (EDSS) progression relative to non-HDA and overall groups (overall population: 18%; HRA and non-HRA: 14% and 20%, respectively; HRA+DAT and non-HRA+DAT: 13% and 21%, respectively). The proportion of patients with confirmed 3- and 6-month EDSS progression was lower in HDA subgroups in CLARITY Ext compared to corresponding subgroups in CLARITY.*

Conclusions: *In CLARITY Ext, long-term sustainability of the clinical effect was observed in HDA patients who were treated with CT3.5 in CLARITY.*

Relativamente alla sicurezza di cladribina, i dati di *real life*, con *follow-up post-marketing* prolungato fino a 10 anni (studi CLARITY, CLARITY Extension, ORACLE e registro PREMIERE), sono del tutto rassicuranti (Poster P875). Dalla loro analisi integrata - aggiornata a luglio 2018 (compresi dati relativi a 6 mesi di commercializzazione in Europa) – si conferma il favorevole profilo di eventi avversi emergenti dal trattamento (TEAE, *treatment emergent adverse events*) già evidenziato negli studi registrativi, in costante assenza di segnalazioni di leucoencefalopatia multifocale progressiva (PML) e di incremento del "rischio oncologico" e con un'incidenza aggiustata "non significativa" di linfopenia grave (grado 3-4 / 0.11-0.12 per 100 pazienti-anno *versus* 0 nei bracci placebo) e di infezioni gravi da *Herpes Zoster* (0,05-0.06 per 100 pazienti-anno *versus* 0 nei bracci placebo).

POSTER P875

Cook S, et al. Updated safety analysis of Cladribine Tablets in the treatment of patients with multiple sclerosis.

Introduction: *Pooling of long-term safety data for integrated analysis allowed comprehensive characterisation of the Cladribine Tablets (CT) safety profile in patients at the earliest stages, or more advanced stages of relapsing multiple sclerosis (RMS). Previous characterisation of a monotherapy oral cohort treated with CT 3.5 mg/kg (CT3.5) included cumulative safety data up to Feb 2015, >3 years beyond completion of the last clinical study.*

Objectives: Two-year update of the serious treatment emergent adverse event (TEAE) profile from the CT3.5 integrated safety analysis.

Methods: *The monotherapy oral cohort was derived from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry. It included 923 patients who received CT3.5 and 641 patients who received placebo (PBO). Adjusted adverse events incidences per 100 patient-years (Adj-AE per 100PY) were calculated. Two data cut-offs were compared: cumulative to Feb 2015 (previously presented, defined here as "Period 1" [P1]) and cumulative to May 2017 (updated, defined as "Period 2" [P2]). Serious adverse drug reactions (ADR; implied causality) from post-marketing sources are also summarised.*

Results: *Demographics at respective study enrolment, including age (36.5 years, CT3.5), proportion of females (66.3%, CT3.5) and prior disease modifying drug experience, were balanced among treatment groups. Adj-AE per 100PY rates for experiencing ≥1 serious TEAE were 3.88 (CT3.5) and 3.24 (PBO) in P2, 4.00 (CT3.5) and 3.57 (PBO) in P1. Adj-AE per 100PY for serious lymphopenia (preferred term [PT]) were 0.11 (CT3.5) and 0 (PBO) in P2, 0.12 (CT3.5) and 0 (PBO) in P1; for serious infection and infestations (system organ class [SOC]): 0.63 (CT3.5) and 0.44 (PBO) in P2, 0.69 (CT3.5) and 0.50 (PBO) in P1; for serious herpes zoster (PT): 0.05 (CT3.5) and 0 (PBO) in P2, 0.06 (CT3.5) and 0 (PBO) in P1. Adj-AE per 100PY for serious neoplasms, benign, malignant and unspecified (SOC) were 0.65 (CT3.5) and 0.35 (PBO) in P2, 0.74 (CT3.5) and 0.50 (PBO) in P1. Regarding post-marketing data, 11 serious ADRs were reported; none are new safety findings for CT3.5.*

Conclusions: *This integrated analysis confirms the serious TEAE profile associated with CT3.5 treatment of patients with early and active RMS. The updated profile (P2) was generally consistent with that from 2 years prior (P1). No new major safety findings were identified in the updated dataset, where patients were followed for up to 10 years.*

Nel complesso i dati di *real life* presentati all'ECTRIMS 2018 contribuiscono a caratterizzare ulteriormente il favorevole profilo di cladribina confermandone:

- l'efficacia prolungata fino a 4-5 anni,

ben oltre la durata dello schema posologico approvato e senza necessità di ulteriore trattamento, anche nei pazienti ad elevata attività di malattia;
- la sicurezza a lungo termine, senza segnalazione di PLM e con una percentuale "non significativa" di linfopenia severa (grado 3-4) – Da notare, a tal proposito, che la sorveglianza *post-marketing* ha registrato in Europa (6 mesi di commercializzazione) soltanto 47 eventi avversi cladribina-correlabili, nessuno dei quali nuovo/inaspettato.

Cladribina emerge quindi come un'opzione preferenziale nei pazienti con SM-RR ad elevata attività ("aggressiva"/in peggioramento) consentendo di ottenere – grazie al suo peculiare meccanismo d'azione - un *reset* immunitario, ovvero una ricostituzione immunitaria selettiva (IRT, *immune reconstitution therapy*) efficace, sicura e duratura, con uno schema posologico "a basso impatto" che di fatto azzera la non aderenza.

Del "valore aggiunto" di cladribina nello scenario terapeutico in rapida evoluzione della SM si è discusso anche in due Simposi dell'ECTRIMS 2018, organizzati con il contributo non condizionante di Merck. Nel primo *(Evolving MS treatment with immune reconstitution therapy)*, i Relatori hanno sottolineato il notevole impatto che l'IRT con cladribina può avere sul trattamento della SM, evidenziando alcuni punti chiave, ovvero:
- la necessità di continuare ad approfondire le nostre conoscenze di fisiopatologia della malattia, essenziali per ottimizzare la decisione terapeutica; in particolare, occorre indagare sulle varie componenti della sequenza patogenetica – neuroinfiammazione, demielinizzazione, perdita assonale, neurodegenerazione - e sul loro "peso" nelle varie fasi evolutive della SM;
- il "rivoluzionario" approccio dell'IRT con cladribina, concettualmente differente dalle attuali DMTs *(disease modifying therapies)* che, di fatto, possono essere tutte classificate come terapie di mantenimento, la cui efficacia clinica necessita di una somministrazione continua; con cladribina, al contrario, è possibile una somministrazione non continua i cui effetti biologici (*reset* immunitario) perdurano ben oltre il periodo di somministrazione;
- il peculiare meccanismo d'azione di cladribina, selettivo su linfociti B e T, che determina transitoria immunodepressione seguita da una ricostituzione linfocitaria che, mantenendo l'immunocompetenza, si caratterizza per favorevoli modificazioni qualitative a lungo termine dell'immunità adattativa;
- il profilo di sicurezza assolutamente favorevole dell'IRT con cladribina, correlato alla possibilità di evitare i rischi associati ad una immunosoppressione/immunomodulazione continua; si consideri inoltre il "basso impatto" dell'IRT con cladribina, sia in termini di posologia sia di monitoraggio clinico-laboratoristico (test ematici, *screening* infezioni).

Nel secondo Simposio Satellite *(Treatment sequencing in MS: how do you choose the right DMD for your patient?)* i contributi si sono focalizzati sul "sequenziamento" e la personalizzazione della terapia, con interessanti dati di *real life* sull'iniziale esperienza con cladribina in Europa e in Australia. In sintesi, i Relatori hanno ribadito:
- l'importanza di un trattamento precoce, raccomandato da tutte le linee guida internazionali;
- la necessità di personalizzare il trattamento perché non esiste una "taglia unica" *(one size fits all)*;

- il ruolo ancora importante dei *platform drugs*, in particolare dell'interferone β-1a sottocute, che ha un profilo di efficacia e sicurezza ben consolidato a 20 anni dalla sua approvazione;
- l'opportunità di considerare nello *switch* a farmaci più potenti non soltanto l'evidenza di attività di malattia e/o di non aderenza alla DMT in atto, ma anche – in condivisone con il paziente - l'impatto *(burden)* dell'*escalation* in termini di posologia e monitoraggio, la sicurezza e la tollerabilità del "seconda linea", gli obiettivi terapeutici che si vogliono raggiungere e l'eventuale volontà di pianificare una gravidanza.

Interferone beta-1a sottocute. Un *platform drug* ancora in prima linea a 20 anni dalla sua approvazione

A 20 anni dalla sua approvazione in Europa, l'interferone beta-1a sottocute (IFNβ-1a sc) resta un farmaco di riferimento nel controllo della sclerosi multipla all'esordio. Tra i tanti contributi presentati all'ECTRIMS 2018, se ne segnalano due di particolare interesse sulla sicurezza dell'IFNβ-1a sc in gravidanza e sulla sua efficacia nel ridurre l'accumulo di lesioni in specifici tratti della sostanza bianca.

I dati aggiornati (Poster P1753), che confermano la sicurezza dell'IFNβ (nelle formulazioni approvate) per gestante e feto, sono quelli dell'European *Interferon Beta Pregnancy Registry* (948 gravidanze con esposizione al farmaco ed *outcomes* riportati, con segnalazioni provenienti dalle industrie farmaceutiche titolari dell'autorizzazione all'immissione in commercio e dai medici curanti) e dei registri di popolazione finlandese e svedese (875 gravidanze con esposizione al farmaco ed *outcomes* riportati). L'esposizione è avvenuta sin dal primo giorno dell'ultimo periodo mestruale, poco prima del concepimento o in corso di gravidanza. L'analisi preliminare evidenzia prevalenze simili di aborto spontaneo, di nati vivi con anomalie congenite e di gravidanze ectopiche rispetto a coorti non esposte, con percentuali in linea con quelle attese nella popolazione generale. Non vi è dunque alcuna evidenza che l'esposizione all'IFNβ prima del concepimento e/o durante la gravidanza abbia un impatto sfavorevole sugli *outcomes* gravidici e neonatali.

POSTER P1753

Hellwig K, et al. Pregnancy and infant outcomes with interferon beta: data from the European Interferon Beta Pregnancy Registry and Population Based Registries in Finland and Sweden

Introduction: *Women with multiple sclerosis (MS) are often diagnosed and treated at childbearing age. Systematic reviews and registry studies suggest that MS and interferon-beta (IFNβ) exposure do not adversely affect pregnancy outcomes; however, data on risks of IFNβ exposure during pregnancy are limited. To address this lack of evidence, a European IFNβ pregnancy registry was established and a population-based cohort study was conducted based on data from two Nordic health registers (Finland and Sweden).*

Objective: *To assess the prevalence of pregnancy and infant outcomes in IFNβ exposed pregnant women with MS from European IFNβ pregnancy registry and Nordic health registers.*

Methods: *In the European IFNβ pregnancy registry, women identified themselves to the Marketing Authorization Holders (Bayer, Biogen, Merck, Novartis) or healthcare professionals as pregnant and exposed to IFNβ since the first day of the last menstrual period (LMP), shortly before conception, or during pregnancy. In the Nordic countries, data were retrospectively analysed from national health registers recording births. Women treated with IFNβ during pregnancy or within three months prior to LMP were considered as exposed. Pregnancy outcomes collected included congenital anomalies, spontaneous abortions, elective pregnancy terminations, ectopic pregnancies, stillbirths and live births. The prevalence of pregnancy outcomes in women exposed to IFNβ in the European registry are presented alongside the Nordic data, and a cohort of women with an MS diagnosis but unexposed to MS treatment from the Nordic dataset.*

Results: *A total of 948 and 875 pregnancy reports with exposure to IFNβ and known pregnancy outcomes were collected from the European registry (Eur) and the Nordic registers, respectively. Preliminary analyses showed similar prevalences of spontaneous abortions versus the non-exposed cohort (10.7% Eur; 7.9% Nordic vs. 11.1%) and similar prevalences of live births with congenital anomalies (1.8% Eur; 1.8% Nordic vs. 3.3%) and ecto-*

pic pregnancies (0.4% Eur; 1.5% Nordic vs. 2.9%); and are also in line with expected rates from the general population. Additional analyses on pregnancy outcomes will be presented.

Conclusions: *The European IFNβ pregnancy registry showed no evidence that IFNβ exposure before conception and/or during pregnancy adversely affected pregnancy or infant outcomes; consistent with data collected from the Nordic registers.*

Un gruppo italiano (Università di Siena) ha invece presentato (ePoster EP1511) i risultati di un'analisi *post-hoc* dei dati di risonanza magnetica dei pazienti arruolati nello studio IMPROVE *(A study to evaluate Rebif® new formulation - interferon-beta1a - in relapsing remitting multiple sclerosis)*. Con metodologia di *lesion probability mapping* (LPM), si è potuto verificare che la dimostrata efficacia dell'IFNβ-1a sc nel ridurre l'accumulo nel tempo di lesioni cerebrali (CUA, *combined unique active lesions*) mostra una differenziazione spaziale che si fa evidente dopo 16 settimane di trattamento. La riduzione di CUA (*vs* placebo) coinvolge infatti prevalentemente specifiche aree della sostanza bianca clinicamente "eloquenti", quali il tratto cortico-spinale (-50% circa), la radiazione talamica anteriore sinistra (-52%) e il fascicolo longitudinale superiore (-65%).

ePOSTER EP1511

Giorgio a, et al. Rapid reduction of lesion accumulation in specific white matter tracts as assessed by lesion mapping in relapsing-remitting MS patients treated with IFN beta-1a.

Introduction: *It is well known that the administration of interferon (IFN) beta-1a in patients with relapsing-remitting (RR) MS reduces brain lesion accumulation over time, as assessed by magnetic resonance imaging (MRI). It is less clear, however, whether such reduction may have treatment-specific spatio-temporal characteristics.*

Objective: *To assess spatio-temporal characteristics of active MRI lesions in patients treated with IFN beta-1a or placebo, by using a lesion mapping approach on monthly-acquired MRI data.*

Methods: *We performed a post-hoc analysis of MRI data in RRMS patients from the IMPROVE study, a randomized (2:1) clinical study (ClinicalTrials.gov identifier NCT00441103) comparing patients treated with IFN beta-1a 44 mcg given subcutaneously three times per week (n=120) versus placebo (n=60). We used MRI examinations acquired at weeks 4, 8, 12 and 16 to create lesion probability maps (LPMs) of the cumulative combined unique active (CUA) lesions in each patient group. At each time-point, differences in lesion location between treated and placebo groups were assessed along several white matter (WM) tracts by using predefined anatomic WM atlases. Differences in lesion frequency were assessed with a voxelwise comparison between treated and placebo groups within the general linear model framework and using nonparametric permutation test (p< 0.05, cluster-corrected).*

Results: *The progressive involvement of the WM area occupied by CUA lesions was half in the treated (41 cm^3 at week 4, 95 cm3 at week 16, mean: 24 cm3/month) than in the placebo group (62 cm3 at week 4, 196 cm3 at week 16, mean: 48 cm3/month). Similar results were obtained with the WM tract analysis, with a reduction of lesion accumulation in the treated group in the order of 50% in the corticospinal tract (CST), 52% in the anterior thalamic radiation (ATR) and 65% in the superior longitudinal fascicle (SLF). At voxelwise analysis, LPM of the treated group showed lower frequency of CUA lesions than that of the placebo group since week 4. This became particularly pronounced at week 16 in the left CST (p< 0.005), left ATR (p< 0.005) and right SLF (p< 0.02).*

Conclusions: *Treatment with IFN beta-1a, in comparison to placebo, rapidly reduces lesion accumulation in RRMS patients along specific WM tracts, reaching the highest local differences in clinically eloquent WM tracts such as CST, SLF and ATR.*

È per certi aspetti curioso osservare che, nel celebrare con nuove significative evidenze il ventennale dell'IFNβ-1a sc, Merck abbia voluto presentare, in una *late-breaking session*, i primi dati clinici (Fase II) su evobrutinib, un nuovo potenziale farmaco orale per la sclerosi multipla recidivante. La scelta dell'industria farmaceutica è tuttavia significativa, testimoniando il suo costante impegno nella ricerca. Evobrutinib è un inibitore, altamente specifico e irreversibile, della tirosin-chinasi di Bruton (BTK), una proteina vitale per la maturazione e la funzionalità di linfociti B e macrofagi e altre cellule immunitarie. Evobrutinib è in effetti progettato in laboratorio per inibire la proliferazione dei linfociti B e il loro rilascio di anticorpi e citochine, senza coinvolgere i linfociti T. In altri termini, l'inibizione della BTK è potenzialmente in grado di sopprimere cellule producenti auto-anticorpi e di risultare quindi terapeuticamente efficace in determinate malattie autoimmuni. Altri inibitori della BTK sono utilizzati in oncologia. Evobrutinib è il primo valutato per una patologia non neoplastica. I primi dati dello studio (NCT02975349 – placebo-controllato, in doppio cieco), relativi a 243 pazien-

ti con SM-RR o SM-SP con recidive "superimposte", che hanno completato le 24 settimane di trattamento - sono stati presentati da Xavier Montalban (sessione scientifica - abstract 322). In sintesi, evobrutinib alla posologia di 75 mg/die o 75 mg due volte/die:

- riduce significativamente il numero di lesioni T1 gadolinio-positive alla risonanza magnetica (*endpoint* primario), con evidenza di una relazione dose-risposta;
- riduce il numero e la rilevanza clinica delle recidive, con un *trend* più significativo per il dosaggio maggiore;
- mostra un profilo di sicurezza maneggiabile (in particolare, incremento asintomatico e reversibile di transaminasi e lipasi, anche in questo caso più frequente al dosaggio maggiore); non si sono comunque registrate infezioni gravi, né linfopenia.

I dati preliminari, che necessitano ovviamente di conferme (a 48 settimane e su coorti più ampie), suggeriscono che il duplice meccanismo d'azione di evobrutinib su linfociti B e macrofagi, che impatta quindi su immunità adattativa e innata, può traslare in efficacia clinica.

SESSIONE SCIENTIFICA (ABSTRACT 322)

Montalban X, et al. Primary analysis of a randomised, placebo-controlled, phase 2 study of the Bruton's tyrosine kinase inhibitor evobrutinib (M2951) in patients with relapsing multiple sclerosis.

Background: *Evobrutinib (M2951) is a highly specific, irreversible, oral inhibitor of Bruton´s tyrosine kinase (BTK) that functionally impairs activation of B-cells and macrophages in vivo and may be effective in autoimmune disease. This study (NCT02975349) evaluated evobrutinib in clinically and radiologically active RMS.*

Methods: *In this double-blind, placebo (PBO)-controlled, 48-wk, Ph 2 study, patients (pts) aged 18-65 years with RRMS or SPMS with superimposed relapses were randomised to evobrutinib 25mg QD, 75mg QD, 75mg BID, PBO or open-label dimethyl fumarate (240mg BID; reference arm). The primary endpoint was the sum of T1 Gd+ lesions at wks 12, 16, 20, and 24. Key secondary endpoints included annualised relapse rate (ARR) at wk 24 and safety. Primary analysis (evobrutinib groups versus PBO) was planned when all pts reached 24 wks of treatment or prematurely discontinued.*

Results: *243 (91%) of 267 randomised pts completed 24 wks of treatment. Baseline characteristics were balanced across groups. Mean (SD) total T1 Gd+ lesions (wks 12-24) was 4.07 (5.76), 5.23 (12.52), 1.69 (4.69) and 1.39 (3.85) in the PBO, evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively. T1 Gd+ lesions per scan were significantly reduced with evobrutinib 75mg QD (lesion rate ratio [RR]=0.38; p=0.01) and 75mg BID (RR=0.48; p=0.05), but not 25mg QD (RR=1.54; p=0.22) vs PBO; a dose-response relationship was seen (p=0.003). A trend towards a reduction in ARR (unadjusted [95% CI]) was seen with evobrutinib 75mg QD (0.13 [0.03-0.38]; p=0.15) and BID (0.08 [0.01-0.30]; p=0.10) vs PBO (0.33 [0.14-0.64]), with evidence of dose-response (p=0.03). Rates of treatment-emergent adverse events (TEAEs) and serious TEAEs were comparable with evobrutinib 25 and 75mg QD and PBO, but higher with evobrutinib 75mg BID (driven by asymptomatic increases in liver transaminases). Grade 3 TEAEs were more frequent with evobrutinib 75mg BID; most were asymptomatic, reversible transaminase elevations with no Hy's Law cases. There were no serious infections with evobrutinib and no other emerging safety signals.*

Conclusions: *The primary endpoint was met, with evobrutinib 75mg QD and 75mg BID significantly reducing the number of T1 Gd+ lesions vs PBO. In this 24 wk analysis, evobrutinib led to numerical and clinically relevant decreases in ARR, with evidence of a dose response and a manageable safety profile. These data support a role for evobrutinib in MS, warranting evaluation in larger trials.*

Sclerosi multipla ad alta attività/progressiva. Nuovi dati su natalizumab, fingolimod e ocrelizumab

Il controllo delle forme di malattia ad alta attività e di quelle progressive resta il più importante bisogno insoddisfatto nella sclerosi multipla. La progressione della disabilità impatta in maniera drammatica sulla qualità di vita della persona malata e di chi se ne prende cura. I *caregivers* sono in realtà dei "pazienti nascosti" e soltanto recentemente si è posta maggior attenzione anche ai loro bisogni nell'ottica di un approccio olistico alla gestione della malattia. Nell'ambito dell'ECTRIMS 2018 è stata annunciata l'imminente pubblicazione dei

risultati di un'indagine mondiale sui *caregivers* di persone con SM. Supportata da Merck, la *survey "Living with multiple sclerosis: the carer's perspective"* (il cui *report* è disponibile *online*) è frutto della collaborazione con l'*International Alliance of Carer Organizations* (IACO) ed Eurocarers, e ha avuto come obiettivo quello di esaminare le esperienze di oltre 1.000 *caregivers* in sette Paesi: Stati Uniti, Canada, Regno Unito, Francia, Germania, Italia e Spagna. Sulla stessa linea di sostegno alle persone malate e, più in generale, di esplorazione dei bisogni insoddisfatti della comunità della SM, Merck ha presentato anche, in prima mondiale, il docufilm *"Seeing MS from the Inside Out"*, che traduce in linguaggio artistico l'esperienza vissuta da chi è toccato dalla patologia. Il documentario, realizzato con la produzione esecutiva del *social network* Shift.ms, racconta le storie di tre persone: Maria Florencia, una paziente argentina con SM; Jon Strum, *caregiver* statunitense; il Dottor Luigi Lavorgna, neurologo italiano. Ciascuno dei protagonisti è stato affiancato da un artista visivo che ha dato vita alla sua storia e ne ha reinterpretato il piano emotivo slegandosi dalla parola e rispecchiando nell'arte la natura della SM, spesso difficile da spiegare.

Relativamente alla terapia farmacologica delle forme di malattia ad alta attività/progressive, si segnalano di seguito alcuni interessanti contributi presentati all'ECTRIMS 2018 su natalizumab, fingolimod e ocrelizumab, ricordando che cladribina "è indicata per il trattamento di pazienti adulti con sclerosi multipla recidivante ad elevata attività, definita da caratteristiche cliniche o di diagnostica per immagini" (vedi anche Riassunto delle Caratteristiche del Prodotto).

Natalizumab

I dati aggiornati di *real life* dello studio osservazionale internazionale Top *(Tysabri Observational Program)*, il più ampio (oltre 6.000 soggetti) attualmente in corso su pazienti trattati con natalizumab, confermano la sua efficacia clinica *(effectiveness)* a lungo termine (10 anni; *follow-up* mediano 63 mesi, con *range* 1-131) nella SM-RR ad alta attività e l'importanza di un avvio precoce del trattamento. I risultati in termini di sicurezza sono conformi al profilo noto e consolidato, senza segnalazione di eventi avversi nuovi/inattesi (Poster P908).

POSTER P908

Kappos L, et al. Real-world data from over 10 years in the TYSABRI® Observational Program: long-term safety and effectiveness of natalizumab in relapsing-remitting multiple sclerosis patients.

Introduction: *The TYSABRI Observational Program (TOP) began >10 years ago to inform on long-term safety and effectiveness of natalizumab (NTZ) in relapsing-remitting multiple sclerosis (RRMS) patients in clinical practice. TOP is the largest ongoing, real-world study of NTZ-treated patients.*

Objectives: *Report an interim analysis of safety and effectiveness in patients with up to 10 years of NTZ treatment in TOP, an open-label, multinational, prospective, observational study.*

Methods: *Annualised relapse rates (ARRs) for the year prior to starting NTZ and on NTZ (and ≤84 days post discontinuation) were compared using a repeated Poisson model. Confirmed Expanded Disability Status Scale (EDSS) worsening, an increase of ≥1.5 from a baseline (BL) of 0, ≥1.0 from a BL of 1.0-5.5, or ≥0.5 from a BL ≥6.0, and improvement, a decrease of ≥1.0 from a BL ≥2.0, while on NTZ were estimated by Kaplan-Meier analysis; confirmation could occur ≤84 days post discontinuation. Serious adverse events (SAEs) were assessed at clinical visits.*

Results: *As of November 2017, TOP included 6149 patients. At BL, mean EDSS score was 3.5; 90.6% had prior disease-modifying therapy (DMT) use. A total of 3210 patients (52.2%) discontinued NTZ; 2118 (34.4%) withdrew from TOP. Median exposure was 38 (range, 1-135) doses; median follow-up time was 63 (range, 1-131) months. ARR while on NTZ was reduced by 89.4% (from 1.99 pre-NTZ to 0.21 on NTZ; P< .001). Similarly, for those with BL EDSS scores < 3.0 or ≥3.0, ARR decreased by 91.0% (P< .001) and 87.9% (P< .001), respectively. For those with 0, 1, or ≥2 prior DMTs, ARRs were reduced by 92.7% (P< .001), 91.0% (P< .001), and 86.7% (P< .001), respectively. At 10 years, cumulative probabilities of 24-week-confirmed EDSS worsening and improvement were 32.9% and 35.5%, respectively. Overall, 828 of 6149 patients (13.5%) experienced ≥1 SAE (most commonly reported by system organ class: infections and infestations, 253 patients [4.1%]).*

Conclusions: *Since the TOP 5-year interim analysis (December 2012), cohort size (N=4821), median exposure (22 doses), and median follow-up time (26 months) have grown, and this analysis reinforces the consistent effectiveness, particularly when used earlier in the disease and treatment course, and the unchanged, established safety profile of NTZ, now assessed over 10 years. The planned continued follow-up for up to 15 years in TOP will provide the longest evaluation of real-world outcomes in NTZ-treated patients.*

Uno studio multicentrico italiano ha peraltro dimostrato che, distanziando le dosi di natalizumab (intervallo medio tra le somministrazioni da 4,5 a 6,3 settimane), non si pregiudica l'efficacia del trattamento (Poster P587).

POSTER P587

Clerico M, et al; TY STOP2 Study Group. Extended interval dosing of natalizumab: is efficacy preserved?

Introduction: *Some clinicians in Italy extended the dose of natalizumab infusions after 24 doses, with the hypothesis of reducing PML risk; this idea was supported by recent reports.*
Objective: *To make this strategy feasible, it is necessary to ascertain the therapeutic durability of the extended dosing strategy.*
Aim: *To evaluate the non-inferiority in controlling disease activity of an extended interval dosing (EID) of natalizumab.*
Methods: *Patients who received natalizumab for at least 24 weeks in 14 Italian centers were included in the analysis. Patients were grouped in 2 categories according to the mean number of weeks between doses (< =5.5 weeks, standard interval dosing (SID);>5.5 weeks, EID). Only the dose intervals before the first relapse was used to estimate the mean intervals between doses, to minimize the bias associated to a possible return to SID in patients under EID after they experienced a relapse. The non-inferiority of EID vs SID was a priori defined as satisfied if the upper limit of the 95%CI of the annualized relapse rate (ARR) in the EID group did not exceed the mean ARR of the SID group by 0.02 relapse/year. Baseline characteristics were comparedbetween groups by aMann Whitney U test. ARR during follow up was estimated and compared between groups by a multivariate Poisson regression model.*
Results: *341 patientswere included in this analysis. The median interval between doses was 4.9 weeks (range 3.7-8.4), with a clear bimodal distribution (modes at 4 and 6 weeks) associated with individual centers strategies (the median was 4.5 weeks in 220 patients from 12 centers and 6.2 in 121 patients from 2 centers). 221 patients were in the SID (median dose interval=4.5 weeks) and 120 in the EID group (median dose interval=6.3 weeks). The ARRduring follow up adjusting for all the baseline variables (age, disease duration, relapses in 2 years pre-natalizumab start, EDSS, number of previous treatments) was 0.042 (95%CI=0.026-0.067) in the SID group, and it was 0.007 (95%CI=0.002-0.028) in the EID group. The non-inferiority of EID vs SID was satisfied.*
Conclusions: *In this cohort there is no evidence of a reduced efficacy of natalizumab by extending the intervals between doses from a median of 4.5 to a median of 6.3 weeks. This observation confirms previous results and together with the emerging evidence of a reduced risk of PML associated to an EID supports the need of a randomized study to change the standard of the natalizumab dosing schedule.*

Lo studio italiano conferma precedenti osservazioni e indica, insieme con le evidenze di un minor rischio di PML correlato ad un distanziamento delle dosi, l'opportunità di un *trial* randomizzato che possa portare ad una modifica, di estrema importanza in termini di sicurezza, dell'attuale schema posologico *standard*.

Fingolimod

Fingolimod è una delle più importanti terapie orali modificanti la malattia, nonché l'unico trattamento della SM recidivante approvato negli Stati Uniti anche in età pediatrica (dai 10 anni). A febbraio 2018, oltre 230.000 pazienti sono stati trattati con l'immunosoppressore orale, per un'esposizione totale di oltre 530.000 pazienti-anno. Di particolare interesse l'analisi *ad interim* dello studio *real world* PANGAEA *(Post-Authorization Non-interventional German sAfety of GilEnyA)*, uno studio tedesco multicentrico, prospettico e non interventistico, mirato a raccogliere dati di efficacia *(effectiveness)*, sicurezza e farmacoeconomia a lungo termine in pazienti con SM-RR trattati con fingolimod (0.5 mg/die) nella pratica clinica quotidiana (Poster P602).
I dati *post-marketing* sulla sicurezza presentati all'ECTRIMS 2018, relativi ad un'osservazione di 5 anni (su oltre 700 pazienti), confermano il profilo favorevole emerso dagli studi registrativi. L'evento avverso più frequente è la linfopenia (11.3%).

POSTER P602

Ziemssen T, et al. Safety of fingolimod in RRMS patients treated for up to 5 years in real world: interim results from the non-interventional PANGAEA study.

Background: *The sphingosine-1-phosphate receptor modulator fingolimod (Gilenya®, Novartis Pharma AG) is an once-daily capsule approved for the treatment of relapsing remitting multiple sclerosis (RRMS). As of February 2018, more than 231.000 patients have been treated with fingolimod; total patient exposure exceeds 536.000 patient-years.*
Objective: *Here we present interim results on the safety of fingolimod and persistency of patients treated with fingolimod for up to 5 years in daily clinical practice in Germany.*

Methods: *PANGAEA is a non-interventional study, conducted in Germany, to investigate long-term safety, effectiveness and patient reported outcomes in daily clinical practice. Recruitment into the study finished in December 2013. In total, 4229 patients were enrolled, of which 726 patients completed the 5 year documentation period by January 2018. The current mean observational period in PANGAEA is 3.02 (±1.83 SD) years representing approximately 12,771 patient years.*

Results: *Yearly study discontinuation ranged between 10.4% and 15.0% over the 5 years of observation. The rate of treatment discontinuation was between 12.3% (1st year) and 8.1% (4th year). 61.7% of patients who started fingolimod treatment between 2011 and 2013 in PANGAEA are still on drug. The most frequent reason for premature study discontinuation (multiple answers possible, 1st vs. 4th year of treatment) was adverse events (AEs; 34.1% vs. 12.9%) followed by patient's decision (23.4% vs. 25.9%) and disease progression (21.3% vs. 32.0%). 87.5% of the patients had no therapy interruption in the documentation period, while 10.6% interrupted treatment with fingolimod once (1.9% more than once). Over the 5 years of observation, the safety profile of fingolimod was comparable to that observed in phase III clinical trials. Commonly reported adverse events were lymphopenia (11.3%), increased liver enzyme levels (5.33%), upper respiratory tract infections (e.g. nasopharyngitis (9.9%)), and potentially MS related adverse events such as fatigue (3.4%) and depression (2.6%). 5.0% of all adverse events were rated serious. 28.3% of the patients experienced no AEs so far.*

Conclusions: *This 5 year interim analysis of PANGAEA provides real world data supportive for the good safety profile of fingolimod demonstrated in phase III clinical trials. The nature of reported adverse events is consistent with previous findings from clinical trials.*

Va inoltre citata l'originale analisi *post-hoc* dello studio registrativo FREEDOMS (FTY720 *Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis* -NCT00289978) e della sua estensione a 4 anni.

L'obiettivo dell'analisi era di verificare, in una sottopolazione di 146 pazienti, il valore predittivo di progressione della disabilità del dosaggio ematico seriato (al basale, quindi a 6, 12 e 24 mesi) dei neurofilamenti leggeri (NFL), rilasciati nei fluidi corporei in seguito a danno neuroassonale (Poster P1227).

POSTER P1227

Kuhle J, et al. An integral measure of serial neurofilament light chain assessments in blood is a predictor of long-term disability progression in relapsing-remitting multiple sclerosis.

Background: *Neurofilament light (NfL) chain is a cytoskeletal protein that is released into the cerebrospinal fluid and eventually in blood following neuroaxonal injury. In relapsing-remitting multiple sclerosis (RRMS), single measurements of elevated NfL concentrations (e.g. at baseline) are correlated with disease activity and are predictive of mid-term lesions and brain atrophy. We hypothesise that an integral measure of several NfL assessments over time may predict long-term disability outcomes in RRMS.*

Objective: *To assess the predictive value of serial NfL assessments collected over 1 or 2 years in reaching time to 6-month confirmed disability progression (6mCDP) and time to Expanded Disability Status Scale score of 4 or more (EDSS≥4).*

Methods: *This post hoc analysis included data from the Phase 3 FREEDOMS trial in patients with RRMS who were randomised to fingolimod 0.5 mg, and continued on the same dose when transitioned into the LONGTERMS extension. The NfL assessments were collected at baseline, and Months 6, 12, 18 and 24 in a subset of patients (N=146). The predictive value of NfL was analysed using a log-rank test and a Cox proportional hazards model with adjustments for sex, age, baseline EDSS, number of relapses in the 2 years prior to study, and quartiles of the geometric mean NfL over 1 or 2 years. The response variable was 6mCDP or time to EDSS≥4 starting after 1 or 2 years. Results are provided with a global log-rank test across all NfL categories, and with a hazard ratio (HR; 95% confidence interval) between the lowest and highest NfL category.*

Results: *Patients with the highest quartile of NfL were twice as likely to have a 6mCDP compared to the lowest quartile when using the geometric mean NfL over 1 year (log-rank test, p=0.0712; Cox: HR=2.0 [0.81; 5.00], p=0.133) and 2.3-times as likely when using the mean NfL over 2 years (p=0.0221; Cox: HR=2.3 [0.77; 6.81], p=0.137). Patients with the highest quartile of NfL were 3.69-times as likely to reach EDSS≥4 compared to the lowest quartile when using the mean NfL over 1 year (p=0.0034; Cox: HR=2.0 [1.31; 10.4], p=0.014) and 8.7-times as likely when using the mean NfL over 2 years (p=0.0007; Cox: HR=2.3 [2.31; 32.6], p=0.0014).*

Conclusion: *NfL in blood fulfils a critical requirement as a prognostic biomarker in MS. It predicts long-term physical disability progression in pa-*

tients with RRMS when taking the mean of several NfL assessments within a period of at least 12 months.

La sottoanalisi evidenzia che un singolo dosaggio dei NFL non ha sufficiente attendibilità prognostica, mentre un calcolo integrale dei dosaggi seriati effettuati nell'arco di almeno 12 mesi è un valido biomarcatore di progressione della disabilità a lungo termine e il suo valore predittivo tende a farsi più robusto quando si allunga il periodo di monitoraggio.

Ocrelizumab

Recentemente approvato anche in Italia, ocrelizumab (OCR) è un anticorpo monoclonale anti-CD20 che sembra offrire nuove possibilità per le forme più aggressive di SM.

Ocrelizumab è infatti indicato "per il trattamento di pazienti adulti affetti da forme recidivanti di sclerosi multipla (SMR) con malattia attiva definita in base alle caratteristiche cliniche o radiologiche... e di pazienti adulti affetti da sclerosi multipla primariamente progressiva (SM-PP) in fase precoce in termini di durata della malattia e livello di disabilità, e con caratteristiche radiologiche tipiche di attività infiammatoria" (vedi anche Riassunto delle Caratteristiche del Prodotto).

Ocrelizumab è quindi il primo e unico farmaco modificante la malattia approvato in Europa per la SM-PP. L'interesse per il nuovo principio attivo è enorme, come testimoniano i numerosi contributi all'ECTRIMS 2018.

Da segnalare l'analisi cumulativa dei dati degli studi registrativi OPERA I e OPERA II [*A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis* – rispettivamente, NCT01247324 e NCT01412333] e della loro fase di estensione *open label* (OLE), nella quale i pazienti continuano OCR (OCR-OCR) o passano *(switch)* da IFNβ-1a a OCR (IFN-OCR). A 5 anni di *follow-up* (2 più 3 del periodo OLE), i risultati dimostrano che (Poster P590):

- la percentuale di pazienti con progressione della disabilità è minore nel braccio OCR-OCR rispetto a quello dei pazienti passati dall'interferone a OCR in fase OLE (braccio IFN-OCR); in altri termini, il trattamento precoce con OCR (due anni prima) correla con una riduzione significativa e sostenuta dell'accumulo di disabilità;
- lo *switching* da IFN a OCR all'inizio della fase OLE correla comunque con una rapida riduzione del tasso annualizzato di recidive, confermando l'importanza di uno *switch* precoce da un "prima linea" che mostri di non essere più in grado di controllare la malattia.

POSTER P590

Hauser SL, et al. Long-term reduction of relapse rate and confirmed disability progression after 5 years of ocrelizumab treatment in patients with relapsing multiple sclerosis.

Background: *The efficacy and safety of ocrelizumab (OCR) in relapsing multiple sclerosis (RMS) were demonstrated in the 96-week double-blind control period of OPERA I and OPERA II (NCT01247324; NCT01412333), and results for the 2-year follow-up of the pooled OPERA I and OPERA II open-label extension (OLE) period have previously been reported (Hauser SL, et al. AAN 2018; Abstract P1.366).*

Objective: *To assess the efficacy of switching to or maintaining OCR therapy on clinical measures of disease activity and progression after 3 years of follow-up in the OLE period of the OPERA I and OPERA II Phase III trials in RMS.*

Methods: *At the start of the OLE period, patients continued OCR (OCR-OCR) or were switched from interferon (IFN) β-1a to OCR (IFN-OCR). Adjusted annualised relapse rate (ARR), time to onset of 24-week confirmed disability progression (CDP24) and change in adjusted mean Expanded Disability Status Scale (EDSS) score from baseline were analysed.*

Results: *Overall, 88.6% of patients who entered the OLE completed OLE Year 3. Among IFN-OCR patients, ARR decreased from 0.20 in the year pre-switch to 0.10, 0.08 and 0.07 at Years 1, 2 and 3 post-switch (p< 0.001, Year 1 vs pre-switch; p=0.31, Year 1 vs Year 2; p=0.56, Year 2 vs Year 3). OCR-OCR continuers maintained the low ARR through the year pre-OLE and the 3 years of the OLE period (0.13, 0.11, 0.08 and 0.07). OCR-OCR continuers versus IFN-OCR switchers had lower proportions of patients with CDP24 in the year pre-switch and Years 1, 2 and 3 of the OLE period (7.7%/12.0%, 10.1%/15.6%, 13.9%/18.1% and 16.1%/21.3%; p< 0.05, all difference comparisons). Changes in mean EDSS scores from baseline in OCR-OCR continuers versus IFN-OCR switchers will also be presented.*

Conclusions: *Switching from IFN to ocrelizumab after 2 years at the start of the OLE period was associated with a rapid reduction in ARR. Both OCR-OCR as well as IFN-OCR patients maintained their robust reduction in ARR through the 3-year follow-up of the OLE period. After 5 years of follow-up, the proportion of patients with disability progression was lower in patients who initiated ocrelizumab treatment earlier (OCR-OCR), compared to patients who received initial IFN treat-*

ment (IFN-OCR switchers), showing that patients who initiated ocrelizumab 2 years earlier accrued significant and sustained reductions in disability progression compared to patients switching from IFN.

Ocrelizumab conferma, dunque, le sue potenzialità nel rallentare in modo significativo la progressione della disabilità nella SM-PP.

Altrettanto interessante una sottoanalisi dello studio ORATORIO (*Ocrelizumab versus placebo in primary progressive multiple sclerosis* - NCT01194570) in una coorte di pazienti con grave disabilità (EDSS ≥6.0) e/o età >45 anni, mirata a verificare l'efficacia di OCR sull'*endpoint* "funzionalità degli arti superiori", misurato con il test dei nove pioli (9-HPT).

I risultati sostanzialmente dimostrano che OCR può ridurre la progressione della disabilità degli arti superiori anche in pazienti con malattia o età più avanzata (Poster 619).

POSTER 619

Giovannoni G, et al. Ocrelizumab treatment effect on upper limb function in PPMS patients with disability: subgroup results of the ORATORIO study to inform the ORATORIO-HAND study design

Background: *It is critically important, for independent daily living, to preserve upper limb function in patients with primary progressive multiple sclerosis (PPMS), especially among those with advanced disability. In the Phase III ORATORIO study (NCT01194570), ocrelizumab (OCR) demonstrated efficacy vs placebo (PBO) in reducing upper limb dysfunction, assessed by 9-Hole Peg Test (9HPT) in PPMS patients with Expanded Disability Status Scale (EDSS) ≤6.5. An important unmet need would be addressed if OCR benefited upper limb function in more disabled PPMS patients ineligible for inclusion in ORATORIO who are more representative of real-world clinical settings.*

Objective: *To assess the effect of OCR on upper limb function in subgroups of more disabled/older patients in ORATORIO, and thereby to inform the design of ORATORIO-HAND, a Phase IIIb, randomised, double-blind, placebo-controlled study in PPMS.*

Methods: *In ORATORIO, PPMS patients (N=732) with EDSS 3.0-6.5, aged 18-55 years were randomised (2:1) to OCR or PBO for ≥120 weeks and until a pre-specified number of EDSS progression events (primary endpoint) occurred. Efficacy of OCR in preventing confirmed 20% worsening in 9HPT was investigated in pre-specified baseline (BL) subgroups of EDSS ≥6.0 and age >45 years, and in an additional subgroup with 9HPT times >25 seconds (s).*

Results: *Subgroup analyses indicate that OCR reduces progression of upper limb disability in more disabled/older PPMS patients: relative risk reduction with OCR vs PBO in 12-week confirmed 9HPT was similar in patients with BL EDSS < 6.0 and ≥6.0 (40% vs 38%, interaction p=0.9187). It was also similar in patients with BL 9HPT ≤25s and >25s (49% vs 44%, interaction p=0.8221); however, 9HPT progression events mainly occurred in patients with 9HPT >25s vs ≤25s (PBO: 34.3% vs 17.8%; OCR: 21.5% vs 9.9%). In patients ≤45 years, OCR showed a weak trend for greater risk reduction for 9HPT progression than those >45 years (52% vs 33%, interaction p=0.2854).*

Conclusions: *Based in part on the observed encouraging treatment effect of OCR on upper limb function, the ORATORIO-HAND study has been designed to further investigate the efficacy of OCR on upper limb function in a rigorous, controlled manner. Eligible patients will be randomised (1:1) to OCR or PBO for ≥120 weeks and until a pre-specified number of confirmed 9HPT progression events (primary endpoint) occur. Key entry criteria include EDSS 3.0-8.0, age 18-65 years, 9HPT >25s. Screening will begin Q4 2018.*

Nello stesso poster gli Autori presentano sinteticamente un nuovo studio specifico di prossimo avvio (ORATORIO-HAND), disegnato *ad hoc* per verificare, in maniera rigorosa, l'efficacia di OCR sulla disabilità degli arti superiori. La perdita di funzionalità degli arti superiori è in effetti molto frequente nei pazienti con SM-PP, e in generale nelle forme aggressive/progressive di SM, e ha un impatto estremamente sfavorevole sulla loro autonomia e qualità di vita, sulla la loro capacità di lavorare, con conseguente incremento anche dei costi sociali della malattia.

A tal proposito, si segnala che, tra i vincitori 2018 del *Grant for Multiple Sclerosis Innovation* (un'iniziativa di Merck, giunta alla 6a edizione), c'è anche una ricercatrice italiana, la Prof.ssa Franca Deriu dell'Università di Sassari, premiata in sede congressuale per il progetto *The effects of eccentric strength training on limb spasticity and muscle weakness in people with MS: a pilot study*. L'eccentric strength training è un tipo di esercizio in grado di migliorare l'attività motoria dei pazienti con SM, riducendone la spasticità e aumentandone la forza muscolare ■