RASSEGNA BIBLIOGRAFICA

a cura della Redazione

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Safety of cladribine tablets in the treatment of patients with multiple sclerosis: An integrated analysis

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Background Treating patients with relapsing multiple sclerosis (MS) with cladribine tablets (two times 4 or 5 days of treatment each year for 2 years) results in long-lasting efficacy, with continued stability in many patients for 4 or more years. Safety and tolerability outcomes from individual clinical studies with cladribine tablets have been reported previously.

Objective Report safety data from an integrated analysis of clinical trials and follow-up in patients with MS to further characterize the safety profile of cladribine tablets.

Methods Data for patients treated with cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg) as monotherapy (n = 923) or placebo (n = 641) in Phase III clinical trials (CLARITY, CLARITY Extension and ORACLE-MS) and followed up in the PREMIERE registry were aggregated (Monotherapy Oral cohort). To better characterize rare events, additional data from earlier studies which involved the use of parenteral cladribine in patients with MS, and the ONWARD study, in which patients were given cladribine tablets in addition to interferon (IFN)-β or placebo plus IFN-β were included in an All Exposed cohort (cladribine, n = 1926; placebo, n = 802). Adjusted adverse events incidences per 100 patient-years (Adj-AE per 100 PY) were calculated for the integrated analyses.

Results The incidence rate of treatment-emergent adverse events (TEAEs) in the Monotherapy Oral cohort was 103.29 vs. 94.26 Adj-AEs per 100 PY for placebo. TEAEs that occurred more frequently with cladribine tablets were mainly driven by the TEAEs of lymphopenia (Adj-AE per 100 PY 7.94 vs. 1.06 for placebo) and lymphocyte count decreased (Adj-AE

per 100 PY 0.78 vs. 0.10 for placebo) as anticipated due to the mode of action of cladribine. An increase in TEAE incidence rate was also observed in the cladribine tablets 3.5 mg/kg group vs. placebo for herpes zoster (Adj-AE per 100 PY 0.83 vs. 0.20, respectively). There were no cases of systemic, serious disseminated herpes zoster attributed to treatment with cladribine tablets. In general there was no increase in the risk of infections including opportunistic infections with cladribine tablets versus placebo, except for herpes zoster. Periods of severe lymphopenia (< 0.5 × 109 cells/L) were associated with an increased frequency of infections, but the nature of these was not different to that observed in the overall patient group treated with cladribine tablets 3.5 mg/kg. Within the constraints of a limited sample size, malignancy rates in the overall clinical program for cladribine in MS did not show evidence of an increase compared to placebo-treated patients and there was no increase in the incidence of malignancies over time in cladribine-treated patients.

Conclusions The AE profile for cladribine tablets 3.5 mg/kg as a monotherapy has been well-characterized in a pooled population of patients from early to more advanced relapsing MS. There was no increased risk for infections in general except for a higher incidence of herpes zoster. Lymphopenia was amongst the most frequently observed TEAEs that occurred at a higher incidence with cladribine relative to placebo. There was also no increase in malignancy rates for cladribine relative to placebo.

Nuove significative conferme sulla sicurezza a lungo termine giungono dai risultati di un'analisi *post-hoc* dei dati di quasi 1.000 pazienti trattati con cladribina orale in monoterapia (*Monotherapy Oral cohort*, *versus* placebo) negli studi CLARITY, CLARITY *Extension* e ORACLE-MS, e poi seguiti nel tempo nel Registro di malattia PREMIERE. Per meglio caratterizzare gli eventi avversi più rari, l'analisi integra anche i dati di studi precedenti con cladribina parenterale o cladribina in combinazione con IFNβ (*All Exposed cohort*, circa 2.000 pazienti). In sintesi:

a) non emerge un incremento del rischio infettivo con cladribina, ad eccezione di una maggiore incidenza di infezioni da *herpes zoster*, peraltro mai gravi e/o disseminate;
b) la linfopenia grave (conta linfocitaria assoluta < 0.5×109 cellulle/L; 25% dei pazienti, in meno dell'1% di grado 4), prevenibile osservando le linee guida di trattamento, incrementa gli eventi avversi infettivi, il cui profilo non differisce tuttavia da quello osservabile fuori da periodi di linfopenia di grado 3-4;
c) non si evidenzia un incremento del rischio di neoplasie. Da notare che i dati sugli eventi avversi emergenti dal trattamento (TEAEs, *Treatment-Emergent Adverse Events*) sono presentati come incidenza *observation-adjusted* per 100 pazienti/anni di esposizione e di *follow-up*, eliminando in tal modo anche i *bias* correlati alla differente durata del *follow-up* nei vari bracci in terapia.

Si segnala infine che nei *supplementary materials*, disponibili *online*, sono presenti dettagli sull'interessante evidenza che, a 4 anni dall'ultima dose di cladribina, soltanto per il 26.8% dei pazienti trattati si è resa necessaria una terapia con un diverso DMD, a conferma ulteriore dell'efficacia persistente di cladribina e delle sue potenzialità di IRT (*Immune Reconstitution Therapy*).

Da marzo 2109 cladribina è stata inserita nella classe di rimborsabilità A, quindi il farmaco è ora a carico del Sistema Sanitario Nazionale.

Comi G, Cook S, Giovannoni G, Rieckmann P, Sørensen PS, Vermersch P, Galazka A, Nolting A, Hicking C, Dangond F.

Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis

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Background Immune reconstitution therapies (IRT) for patients with multiple sclerosis are used for short, intermittent treatment periods to induce immune resetting and allow subsequent treatment-free periods. Cladribine tablets are postulated to be an IRT that causes selective and transient reductions in CD19+ B cells and T cells, followed by reconstitution of adaptive immune function.

Objective To characterize long-term lymphocyte count changes in pooled data from the 2-year CLARITY and subsequent 2-year CLARITY Extension studies, and the PREMIERE registry (Long-term CLARITY cohort).

Methods Data from patients randomized to placebo (n = 435) or cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg; n = 685) in CLARITY or CLARITY Extension, including time spent in the PREMIERE registry were pooled to provide long-term follow-up data. The study investigated absolute lymphocyte counts (ALC) up to 312 weeks and B and T cell subsets up to 240 weeks after the first dose, in patients receiving placebo or cladribine tablets 3.5 mg/kg administered as two short (4 or 5 days) weekly treatments at the start of months 1 and 2 in each treatment year, followed by no further active treatment.

Results Treatment with cladribine tablets 3.5 mg/kg resulted in selective reductions in B and T lymphocytes. Lymphocyte recovery began soon after treatment in each of years 1 and 2. Median ALC recovered to the normal range and CD19+ B cells recovered to threshold values by week 84, approximately 30 weeks after the last dose of cladribine tablets in year 2. Median CD4+ T cell counts recovered to threshold values by week 96 (approximately 43 weeks after the last dose of cladribine tablets in year 2). Median CD8+ cell counts never dropped below the threshold value.

Conclusions These results show the dynamics of lymphocyte count changes following treatment with cladribine tablets 3.5 mg/kg. The immune cell repopulation results provide further evidence that cladribine tablets may represent a form of IRT.

Dall'analisi cumulativa dei dati a lungo termine degli studi registrativi CLARITY e CLARITY *Extension* e del Registro di malattia PREMIERE (*Long-term CLARITY cohort*) emergono ulteriori evidenze sulla peculiarità d'azione di cladribina orale, a conferma delle sue caratteristiche di IRT (*Immune Reconstitution Therapy*).

In particolare, sono state monitorate la conta linfocitaria assoluta fino a 6 anni (312 settimane) dalla prima somministrazione e quelle dei linfociti B $CD19^+$ e T $CD4^+$ fin quasi a 5 anni (240 settimane). Dopo i brevi cicli di cladribina, le conte linfocitarie iniziano precocemente a risalire (ripopolamento cellulare), con il raggiungimento dei valori basali dopo circa 30 settimane dall'ultima assunzione per i $CD19^+$ e 43 settimane per i $CD4^+$. Da notare che:

a) il recupero dei linfociti B non eccede mai la soglia basale, dato che potrebbe dar ragione dell'assenza con cladribina di autoimmunità B-mediata, osservata invece con altri DMDs;
b) i linfociti T $CD4^+$ hanno un recupero più lento, ma senza che emerga un rischio di infezioni opportunistiche che pure ci si potrebbe attendere per la deplezione protratta dei T;
c) come dimostrato da altri studi, l'efficacia del farmaco è mantenuta durante il ripopolamento, senza evidenza clinico-radiologica di una ripresa dell'attività di malattia.

Gli Autori, nel segnalare che le conte mediane dei linfociti T $CD8^+$ (*suppressor*-citotossici) non calano mai sotto i valori basali, annunciano la pubblicazione di un altro *report*, più dettagliato e integrato con i dati dello studio ORACLE-MS, sugli effetti immunofenotipici della cladribina.