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Cladribine tablets are approved in Europe for the treatment of adults with highly active relapsing multiple sclerosis (MS). In general, in the EU, product labels may be too broad to provide recommendations on individual treatment options, leaving clinicians with many unanswered practical questions. Here we describe a consensus-based programme led by international MS experts with the aim of providing practical recommendations to support physicians in the use of cladribine tablets in real-life clinical practice.

Clinical recommendations were developed using a modified-Delphi consensus methodology by a steering committee (SC) of 9 international MS experts. The SC identified practical clinical questions concerning the use of cladribine tablets and a prioritisation exercise selected the 11 most important questions to answer. Statements to address each question were drafted using evidence obtained from a comprehensive literature search, a review of available evidence, and practical experiences and expert perspectives from SC members. An additional 33 faculty were invited to answer the questions via an online platform. Consolidated answers were reviewed and incorporated into clinical recommendations by the SC. Consensus on recommendations was achieved when ≥75% of respondents expressed an agreement score of 7–9, on a 9-point scale.

Consensus was achieved on 46 out of 47 clinical recommendations (n=34). Consensus in the range of 90–100% was achieved on 34/46 recommendations, 10 recommendations achieved 80–90% consensus and 2 recommendations achieved 75–80% consensus. The strength of recommendations ranged from 7–9. The one statement failing to achieve consensus scored 60.6%. Expert-agreed practical recommendations are provided on topics including: the definition of highly active disease; the patterns of treatment response and suboptimal response with cladribine tablets; and switching to and from cladribine tablets.

These expert recommendations provide up-to-date relevant guidance on the use of cladribine tablets in clinical practice.

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Efficacy of a Fourth Alemtuzumab Course in RRMS Patients from CARE-MS II Who Experienced Disease Activity After Three Prior Courses

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In RRMS patients with inadequate response to prior therapy, 2 alemtuzumab courses (12 mg/day; baseline: 5 days; 12 months later: 3 days) significantly improved outcomes versus SC IFNB-1a over 2 years (CARE-MS II [NCT00548405]). Efficacy remained durable in a 4-year extension study (NCT00930553); patients could receive as-needed alemtuzumab retreatment (≥12 months apart) for disease activity, or another disease-modifying therapy (DMT). Through Year 6, 88% remained on study; 50% received neither alemtuzumab retreatment nor another DMT; 16% received ≥4 courses; 3% received ≥5 courses. The objective was to evaluate Course 4 (C4) efficacy in RRMS patients receiving ≥4 courses of alemtuzumab.

Annualized relapse rate (ARR); improved/stable Expanded Disability Status Scale (EDSS) score (versus baseline); 6-month confirmed disability improvement (CDI). 11% of patients met inclusion criteria: ≥4 courses within 60 months of baseline; no DMT. Those receiving C5 were censored at that time.

ARR decreased after C4 (12 months pre-C4 [-12M]: 0.75; 12 months post-C4 [+12M]: 0.19; P<0.0001), remaining low (0.23) at Year 3 post-C4. More patients had stable/improved EDSS scores +12M (67.5%) versus at C4 administration (53.5%). Percentage of patients with CDI increased post-C4 (-12M: 10.0%; +12M: 26.7%).

C4 reduced relapses and stabilized/improved disability in patients with disease activity after initial treatment (C1, C2) plus one additional course (C3).

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Second-Line Therapy in Multiple Sclerosis

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Multiple sclerosis (MS) patients with breakthrough disease on immunomodulatory drugs are frequently offered to switch to second-line treatment (SLT). No head-to-head study has been performed yet to assess whether SLT is more effective than classical immunomodulators. We aim to retrospectively assess the moment of introduction, efficacity and tolerance of SLT.

We retrospectively enrolled the patients in our department with relapsing-remitting MS (RRMS) who received first-line treatment (FLT) for more than 12 months than switched to SLT for 5 consecutive years. Outcome measures were Rio Score (RS) and modified Rio Score (MRS), annualized relapse rate (ARR) and changes in expanded disability status scale (EDSS) score. We also reported the side effects developed under SLT.

We enrolled 20 patients, 6 males and 13 females. They all received interferon before switch. Twelve were switched to Natalizumab (NAT) and eight to Fingolimod (FIN). When switch was decided, 16 patients (80%) had high RS (2 or 3) and 19 (95%) had high MRS (2 or 3). Mean ARR was at 2.4 at the switch to SLT, it decreased significantly to 0.73 (70%) after 12 months and 0.4 (84%) after 5 years (p< 0.001). Nine patients were relapse-free after 12 months (75%) and 5 after 5 years (25%). Mean EDSS was at 3.36 at the switch to SLT, it significally decreased to 3 after 12 months and 1.5 after 5 years (p< 0.001). Side effects reported in 6 cases (30%); 3 cases of lymphopenia under FIN, 2 cases of lymphocytosis and on case of BK virus urinary infection under TYS.

MRS was better to predict suboptimal interferon responders than RS in our study. SLT was more effective than interferon on disease progress and activity during the first 5 years of treatment. However, prospective head to head studies are needed to get higher evidence level.

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Improvements Across Functional Systems Are Maintained Regardless of Early VS Late Confirmed Disability Improvement: CARE-MS 6-Year Follow-Up

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In CARE-MS studies (NCT00530348; NCT00548405), alemtuzumab showed significant improvement vs SC IFNB-1a in clinical/MRI outcomes over 2 years in patients with RRMS, including higher rates of confirmed disability improvement (CDI). Efficacy was maintained in a 4-year extension (NCT00930553). In CARE-MS II, 71% of patients with CDI achieved improvements in >1 EDSS functional system (FS) score; improvements were seen across all FS. The objective was to assess CDI occurring early/late after alemtuzumab initiation in pooled CARE-MS I and II patients over 6 years, including maintenance of effect and pattern of improvement across FS scores.

Patients received two annual courses of alemtuzumab 12 mg/day (baseline: 5 consecutive days; 12 months later: 3 consecutive days) in the core CARE-MS studies, with as-needed alemtuzumab retreatment/other disease-modifying therapies in the extension. CDI was defined as ≥1-point EDSS decrease confirmed over 6 months. Analyses: percentage of patients with improved/stable EDSS scores from baseline to Y6, and with stable/improved or number of improved FS scores at 6 months post-CDI onset.

171/427 (40%) eligible patients achieved CDI, 60% of whom had EDSS scores that remained improved at Y6; 67% of patients without CDI had stable EDSS scores from baseline–Y6. EDSS improvement/stability at Y6 vs baseline was apparent in patients with early CDI (61%/34%) and late CDI (57%/37%), respectively. At 6 months post-CDI onset, improvement/stability in each FS was observed in 90–100% of patients with early/late CDI; improvement was most frequently in sensory, pyramidal, and cerebellar FS. 74%/18% of CDI patients (early) and 67%/13% (late) achieved improvements in >1 FS/≥4 FS, respectively.

CDI, occurring within the first 2 years or later, was maintained at Y6 in absence of continuous treatment and was associated with improvements across multiple FS, indicating a broad and prolonged effect of alemtuzumab on disability improvement, potentially changing the MS disease course.

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Efficacy and Safety of Ocrelizumab in Patients with Relapsing-Remitting Multiple Sclerosis with a Suboptimal Response to Previous Disease-Modifying Therapies (1-Year Interim Results)

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Patients with relapsing-remitting multiple sclerosis (RRMS) often experience disease activity despite receiving a disease-modifying therapy (DMT). The aim of the prospective, multicentre, single-arm Phase IIIb CASTING study (NCT02861014) is to evaluate the efficacy and safety of ocrelizumab (OCR) in patients with RRMS who had a suboptimal response to an adequate course of 1 or 2 DMTs.

Patients in CASTING (Expanded Disability Status Scale [EDSS] ≤4.0; disease duration ≤10 years; discontinued prior DMT of ≥6 months' duration due to suboptimal disease control) received intravenous OCR 600 mg/24 weeks (first dose, 2 × 300 mg, 14 days apart) for 96 weeks. The proportion of patients with NEDA was measured by an absence of protocol-defined relapses (PDRs), 24-week confirmed disability progression (24W-CDP), T1 gadolinium-enhancing lesions and new/enlarging T2 lesions and were calculated using the modified intent-to-treat population (mITT; patients receiving any dose who discontinued early without a protocol-defined event were imputed as having an event if the treatment discontinuation reason was lack of efficacy or death; others were excluded). MRI outcomes were rebaselined at Week 8 (prespecified analyses).

A total of 680 patients (female, 64%; mean [SD] baseline EDSS score, 2.1 [1.1]; disease duration, 5.0 [2.7] years; pretreated with one DMT, n=411 [60.5%]; pretreated with two DMTs, n=265 [39.5%]) were enrolled in CASTING, most commonly for reasons of relapse on prior DMT, and are included in the mITT population. At Week 48, most patients had NEDA (N=586/674 [86.9%]). Rates of 24W-CDP (N=32/673 [4.8%]), PDR (N=28/674 [4.2%]), T1 gadolinium-enhancing lesions (N=19/673 [2.8%]) and new/enlarging T2 lesions (N=42/673 [6.2%]) were generally low; MRI outcomes were rebaselined at Week 8. The adjusted annualised relapse rate (negative binomial model) was 0.048. A total of 591 patients (86.9%) experienced ≥1 adverse event, and 34 patients (5.0%) experienced ≥1 serious adverse event (includes infusion-related reactions).

Most patients in CASTING had no evidence of MS disease activity. As future data become available and are reported, CASTING will describe additional data on the efficacy and safety of ocrelizumab treatment in patients who had ongoing disease activity while receiving another DMT.

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