The proportion of patients with new or enlarged Gd+, T2 lesions, and T1 lesions was significantly lower with alemtuzumab (≤20%) than IFN-β-1a in the core portion of the study (all $P<.0001$) [Coles AJ et al. *Lancet*. 2012], and the proportion in the extension phase in the 20% of patients who received alemtuzumab was comparable. Furthermore, the mean change in brain parenchymal fraction (BPF) from baseline through year 3 was significantly less in alemtuzumab-treated patients, with the year 2 value maintained at year 3, than in IFN-β-1a-treated patients ($P=.012$).

Subgroup analyses revealed that the risk of Gd+ lesions was significantly lower with alemtuzumab compared with IFN-β-1a ($P<.05$ for overall population) for most parameters, with only nonwhite race and Latin American geographic region being equivocal.

Other subgroup analyses based on the same parameters revealed that, compared with SC IFN- β -1a, alemtuzumab significantly lessened the risk of new or enlarging T2 lesions ($P<.01$) and new T1 lesions ($P<.05$) at year 2. Also, the subgroup analysis of the change from baseline in BPF consistently revealed the reduced loss in volume associated with alemtuzumab-treated patients. The difference in volume loss between the alemtuzumab and IFN-β-1a groups was significant for the parameters of patients aged <34 years ($P=.0126$), white race ($P=.0285$), baseline EDSS score ≥2.5 ($P=.0437$), baseline BPF ≥0.816105 ($P=.0359$), baseline T2 lesion volume <5.7135 cm^3, disease duration <3.8 years ($P=.0142$), and no prior SC IFN-β-1a use ($P=.0076$).

The latest findings strengthen support for the superiority of using alemtuzumab in the treatment of active relapsing-remitting MS in patients who have relapsed.

Results of DECIDE: DAC HYP Superior to IFN-β-1a for RRMS

Written by Brian Hoyle

Ludwig Kappos, MD, University Hospital, Basel, Switzerland, described the results of the phase 3, randomized, double-blind, double-dummy, active-controlled Efficacy and Safety of Daclizumab High Yield Process Versus Interferon β 1a in Patients With Relapsing-Remitting Multiple Sclerosis trial [DECIDE; NCT01064401] establishing the superiority of the humanized monoclonal antibody, daclizumab high-yield process (DAC HYP), to interferon beta-1a (IFN-β-1a) in the treatment of relapsing-remitting multiple sclerosis (RRMS).

DAC HYP selectively binds to a subunit of CD25 that is exuberantly expressed on T-cells that become abnormally activated in MS [Perry JSA et al. *Sci Transl Med*. 2012; Wuest SC et al. *Nat Med*. 2011; Martin JF et al. *J Immunol*. 2010; Bielekova B et al. *Proc Natl Acad Sci USA*. 2004; McDyer JF et al. *J Immunol*. 2002]. DAC HYP modulates interleukin-2 signaling without causing general immune cell depletion.

DECIDE was designed to determine if DAC HYP would provide superior outcomes for identified clinical end points compared with IFN-β-1a in greater than 1800 people with RRMS in 28 countries randomized to treatment with subcutaneous DAC HYP 150 mg every 4 weeks (n=919) or intramuscular injection of IFN-β-1a 30 µg QW (n=922). The primary end point was the reduction in annualized relapse rate (ARR). Secondary end points included the number of new or newly enlarging T2 hyperintense lesions on magnetic resonance imaging (MRI), the proportion of patients with sustained disability progression as determined by Extended Disability Severity Scale (EDSS) scores, the proportion of relapse-free patients, and a worsening physical impact score on the MS Impact Scale (MSIS-29).

Baseline demographic and clinical characteristics (duration of RRMS, relapses in previous year, EDSS score, prior treatment, the presence and number of gadolinium-enhancing [Gd+] lesions, and T2 lesions) were similar in both study arms.

The primary end point was met. ARR in the DAC HYP arm was 45% less than in the IFNβ-1a arm (0.216 vs 0.393; 95% CI, 35.5% to 53.1%; $P<.0001$). Significantly, more patients receiving DAC HYP remained relapse-free throughout the trial (overall RR 41%, $P<.0001$), with increasing divergence between the arms with time.

Week 96 MRI data revealed a reduction in the mean number of new and newly enlarged T2 lesions with DAC HYP (9.4 with IFN-β-1a, n=841 vs 4.3 with DAC HYP, n=864; 54% reduction), new Gd+ lesions (1.0 with IFN-β-1a, n=909 vs .4 with DAC HYP, n=900; 65% reduction), and new T1 hypointense lesions (4.4 with IFN-β-1a, n=908 vs 2.1 with DAC HYP, n=899; 52% reduction; all $P<.0001$).

Confirmed disability progression was lower in the DAC HYP arm vs IFN-β-1a, with a risk reduction of 16% ($P=.16$) at 3 months in patients with suspected disease progression and 27% ($P=.0332$) at 6 months in patients with confirmed disease progression; a similar pattern was seen in patients with suspected and confirmed progression with further divergence of the study arms out to week 144. More patients treated with IFN-β-1a than with DAC HYP had MSIS-29 scores that were indicative of a clinically meaningful worsening of symptoms (23% vs 19%; 24% reduction; $P=.0176$). Finally, annualized brain volume change for weeks 0 to 24 and weeks 24

to 96 was lower with DAC HYP (0.67%; $P = .0325$ and 0.52%; $P < .0001$, respectively) vs IFN-β-1a (0.74% and 0.56%, respectively).

The number of adverse events and discontinuation rate were comparable in both arms. DAC HYP was associated with more overall serious adverse events (n = 40, 4%) than IFN-β-1a (n = 15, 2%), with more serious cutaneous events (n = 14, 2% vs n = 1, < 1%), and with more hepatic laboratory abnormalities (n = 59, 6% vs n = 31, 3%). These were manageable with standard monitoring and medical interventions. Discontinuation due to adverse events was higher in the DAC HYP arm (130, 14% vs 81, 9%), whereas the number of deaths was less (4 vs 1).

The researchers concluded that the DECIDE findings support the potential of DAC HYP as a once-monthly option for the treatment of patients with RRMS.

HspB5 Improves MRI Lesions and Clinical Relapse in RRMS

Written by Emma Hitt Nichols, PhD

In patients with relapsing-remitting multiple sclerosis (RRMS), bimonthly injection with low-dose αB-crystallin (HspB5) resulted in a decrease in gadolinium-enhancing (Gd+) lesions and clinical relapses as compared with the placebo. Hans van Noort, PhD, Delta Crystallon, Leiden, the Netherlands, presented data from a randomized study [2011-004475-36; van Noort JM et al. ACTRIMS/ECTRIMS 2014 (poster P082)] that evaluated HspB5 for the treatment of RRMS.

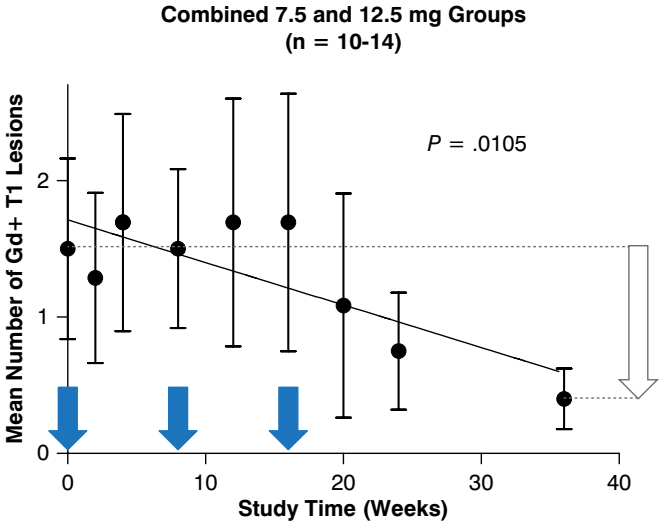
The oligodendrocytes of patients with MS have high levels of HspB5, a glial stress protein that initiates local anti-inflammatory, neuroprotective, and tolerogenic innate responses [van Noort JM et al. *J Neuropathol Exp Neurol.* 2010; Ousman SS et al. *Nature.* 2007]. However, interferon-gamma-secreting Th1 memory cells that target HspB5 exist [van Noort JM et al, *Nature.* 1995; Ousman SS et al. *Nature.* 2007; Bajramović JJ et al. *J Immunol.* 2000], which results in interferon-gamma-induced tissue damage [Bsibsi M et al. *Acta Neuropathol.* 2014]. In a previous Phase 1 study, administration of a single injection of HspB5 to healthy subjects led to an antigen-specific decrease in T-cell responses. The purpose of this study was to further evaluate low doses of HspB5 in patients with RRMS.

In this double-blind phase 2a trial, 32 patients with RRMS were randomly assigned in a 1:1:1:1 fashion to receive 7.5, 12.5, or 17.5 mg of HspB5 or placebo, with follow-up continuing until 48 weeks. HspB5 was administered as 3 bimonthly intravenous injections given at the beginning of the study (week 0), and at week 8 and week 16. At baseline, among the 4 study arms, the mean Extended Disability Severity Scale (EDSS) score ranged from 3.13 to 3.81, the mean number of relapses over the past 2 years from 1.75 to 2.25, and the mean time since the last relapse from 3.32 to 4.23 months.

In patients who received HspB5, there was a trend toward a decrease in Gd+ T1 lesions in all HspB5 arms, as determined by magnetic resonance imaging (MRI), with the 7.5-mg dose of HspB5 resulting in a significant reduction ($P = .017$) over 36 weeks. When the data from the 7.5-mg and 12.5-mg HspB5 groups were combined, the MRI lesion load decreased by 75% at 36 weeks ($P = .0105$; Figure 1) compared with the placebo. After the last dose of HspB5 administered at 16 weeks, the reduction in MRI lesion load continued for 20 weeks. In addition, there was a similar reduction in the frequency of clinical relapses over the 36 weeks among the treatment arms. All doses of HspB5 were safe and well tolerated.

In conclusion, the results of this trial suggest that low-dose HspB5 is safe and well tolerated and may be effective in reducing MRI lesions and clinical relapses in patients with RRMS.

Figure 1. Effect of HspB5 Injection on MRI Lesion Load in RRMS



HspB5, alpha B-crystallin; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis.

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