Lymphocyte Counts in Patients Receiving Daclizumab HYP in DECIDE

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INTRODUCTION

- Daclizumab high-yield process (DAC HYP) selectively blocks interleukin 2 receptor signalling, leading to inhibitory effects on pro-inflammatory effector T cell activities and increased immune regulatory CD56^{bright} natural killer (NK) cells.[1,2]
- In the dose-finding Phase 2 SELECT study, patients with relapsing-remitting multiple sclerosis (RRMS) receiving DAC HYP 150 mg subcutaneous (SC) had modest mean reductions in circulating CD4$^+$ and CD8$^+$ T cell counts (–7.0% and –9.1%, respectively)[3] and mean blood CD56^{bright} NK cell counts were ~500% higher vs. Baseline by Week 52.[2]
- DECIDE was a randomised, double-blind, active-controlled study in which patients with RRMS were randomised to DAC HYP 150 mg SC every 4 weeks (n=919) or interferon (IFN) beta-1a 30 mcg intramuscular (IM) once weekly (n=922) for at least 96 weeks and up to a maximum of 144 weeks.[4]

OBJECTIVE

- To assess changes in total lymphocyte, effector T cell and regulatory CD56^{bright} NK cell counts in relationship to infection status in patients during the DECIDE study.

METHODS

- Whole blood samples were collected and analysed for: total lymphocyte count using complete blood count differential and CD4$^+$ T cell, CD8$^+$ T cell and CD56^{bright} NK cell counts using fluorescence-activated cell sorting with TruCOUNTS (BD Biosciences, San Jose, CA, USA) with validated assays from the laboratories of the contract research organisation.
- In patients receiving DAC HYP, the association between infection status and blood cell counts was evaluated.

RESULTS

- At Baseline, total lymphocyte count and differential counts of CD4$^+$ T cells, CD8$^+$ T cells and CD56^{bright} NK cells were similar between groups. (Table)

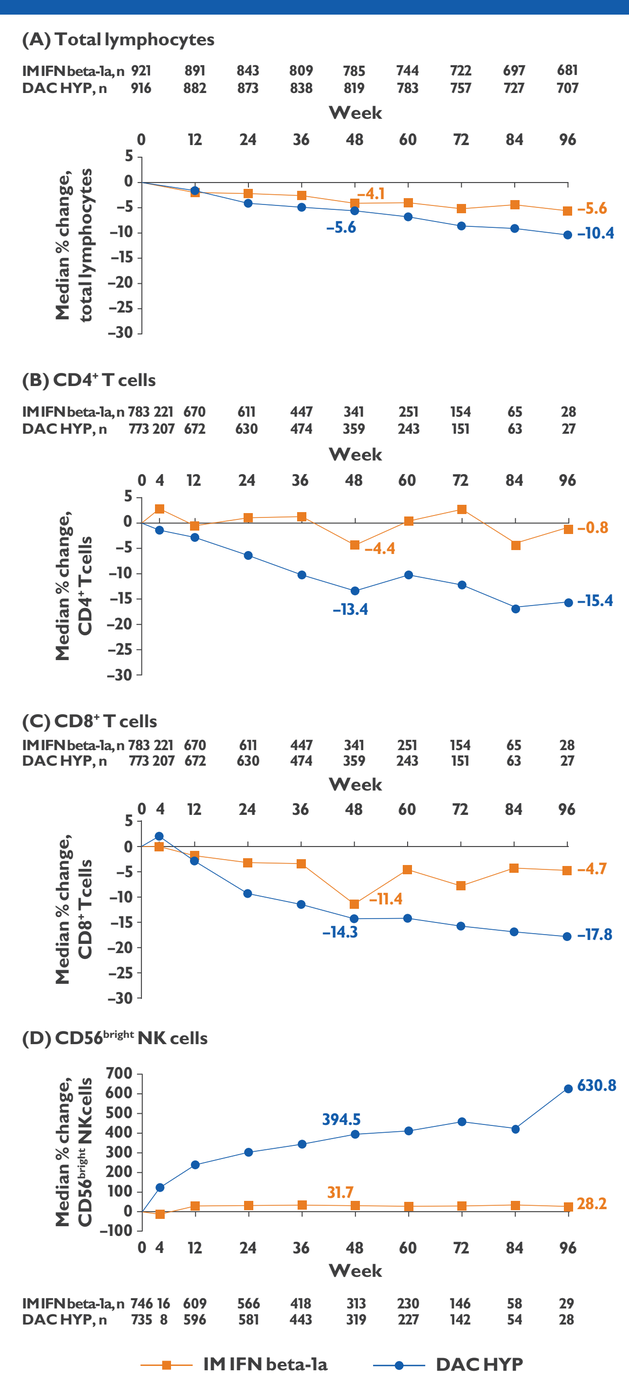
Table. Baseline demographics and disease characteristics

Characteristic	IM IFN beta-1a n=922	DAC HYP n=919
Mean (SD) age, y	36.2 (9.3)	36.4 (9.4)
Female, n (%)	627 (68)	625 (68)
Mean (SD) time from diagnosis, y[a]	4.1 (4.7)	4.2 (5.0)
Mean (SD) no. of relapses within previous year	1.6 (0.8)	1.5 (0.7)
Mean (SD) EDSS score	2.5 (1.3)	2.5 (1.2)
Previous DMT, n (%)[b]	376 (41)	380 (41)
Mean (SD) no. of Gd$^+$ lesions[c]	2.3 (5.9)	2.0 (5.9)
No. with any Gd$^+$ lesion, n (%)	414 (45)	398 (43)
Mean (SD) no. of T2 lesions[d]	51.8 (37.4)	49.2 (35.5)
Median (min, max) total lymphocytes,[e] x 10^9 cells/L	1.830 (0.54, 4.77)	1.840 (0.38, 6.05)
Median (min, max) CD4$^+$ T cells,[f] cells/mm^3	677.0 (40.0, 1831.0)	677.0 (46.0, 2243.0)
Median (min, max) CD8$^+$ T cells,[f] cells/mm^3	337.0 (17.0, 1743.0)	330.0 (36.0, 1739.0)
Median CD4$^+$/CD8$^+$ ratio[f]	2.00	2.05
Median (min, max) CD56^{bright} NK cells,[g] cells/mm^3	11.5 (1.2, 95.7)	11.6 (0.0, 95.6)

DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; Gd$^+$ = gadolinium-enhancing; max = maximum; min = minimum
[a]Time since MS diagnosis
[b]Includes IFN beta, glatiramer acetate, natalizumab, mitoxantrone, azathioprine, fumaric acid, laquinimod, cyclophosphamide, mycophenolic acid, fingolimod, teriflunomide, methotrexate, alemtuzumab, cladribine, immunoglobulins, temsirolimus
[c]IM IFN beta-1a, n=909; DAC HYP, n=900
[d]IM IFN beta-1a, n=908; DAC HYP, n=900
[e]IM IFN beta-1a, n=921; DAC HYP, n=916
[f]IM IFN beta-1a, n=783; DAC HYP, n=773. [g]IM IFN beta-1a, n=746; DAC HYP, n=735

- Median percentage decreases from Baseline in total lymphocyte count (Figure 1A) and CD4$^+$ and CD8$^+$ T cell counts (Figure 1B, C) were greater in the DAC HYP group compared with the IM IFN beta-1a group over 96 weeks of treatment, but these decreases were modest (< 10.5% for total lymphocytes and < 20% for both CD4$^+$ and CD8$^+$ T cell counts).
- Over the treatment period, a small (~30%) median percentage increase in CD56^{bright} NK cells was observed in the IM IFN beta-1a group, while a much larger (~600%) median percentage increase was observed in the DAC HYP group. (Figure 1D)

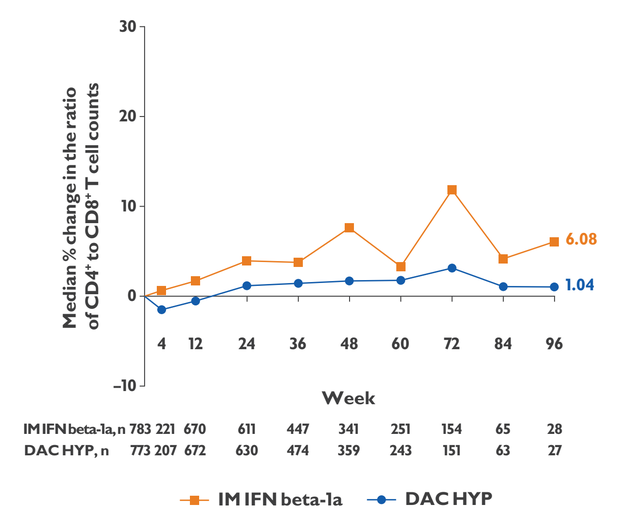
Figure 1. Median percentage change from Baseline in blood cell counts in the DAC HYP and IM IFN beta-1a groups



Four-week data not available for total lymphocyte cell counts

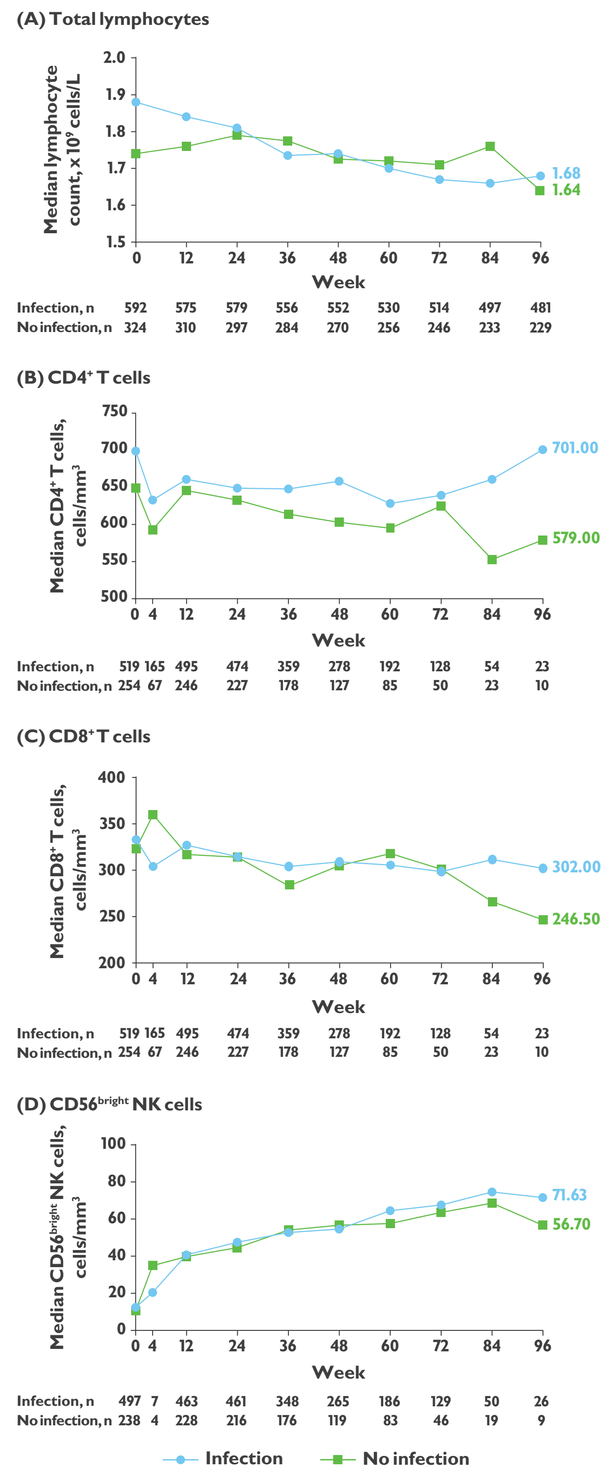
- The ratio of CD4$^+$ to CD8$^+$ T cell counts was stable in the DAC HYP and IM IFN beta-1a groups over 96 weeks. (Figure 2)

Figure 2. Median percentage change from Baseline in the ratio of CD4$^+$ to CD8$^+$ T cell counts



- Median values of total lymphocyte, CD4$^+$ T cell, CD8$^+$ T cell and CD56^{bright} NK subset cell counts in patients receiving DAC HYP who experienced an infection were similar to those who did not. (Figure 3A–D)

Figure 3. Median blood cell counts in patients receiving DAC HYP who experienced or did not experience an infection in DECIDE



CONCLUSIONS

- In the Phase 3 DECIDE study, patients treated with DAC HYP and IM IFN beta-1a showed modest decreases in total lymphocyte, CD4$^+$ and CD8$^+$ T cell counts, and did not show evident changes in the ratio of CD4$^+$ to CD8$^+$ T cell counts over 2 years of treatment.
- Over the treatment period, a large increase in CD56^{bright} NK cells was observed in the DAC HYP group, while a small increase was observed in the IM IFN beta-1a group.
- Results for the DAC HYP group in the Phase 3 DECIDE study are consistent with those reported in a previous placebo-controlled pivotal study.[3]
- Data from the Phase 3 DECIDE study do not show evidence for an association between the occurrence of infections and total lymphocyte, T cell or CD56^{bright} NK cell counts in DAC HYP-treated patients.

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Disclosures

HW: consulting fees/honoraria from Bayer HealthCare, Biogen, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Genzyme and Teva; grants from and contracts with Bayer HealthCare, Biogen, Deutsche Forschungsgesellschaft, the Else Kröner Fresenius Foundation, the German Ministry for Education and Research, the Hertie Foundation, the Interdisciplinary Center for Clinical Studies in Münster, Germany, Merck Serono, Novartis, the NRW Ministry of Education and Research, the RE Children's Foundation, Sanofi-Genzyme and Teva; G Giovannoni: research grant support from Bayer HealthCare, Biogen, GW Pharmaceuticals, Merck Serono, Merz, Novartis, Sanofi-Aventis and Teva; advisory boards/steering committees/monitoring committees for AbbVie Biotherapeutics Inc., Bayer HealthCare, Biogen, Canbex, Eisai, Elan, Five Prime Therapeutics, Genentech, Genzyme, GlaxoSmithKline, GW Pharmaceuticals, Ironwood, Merck Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB and Vertex; SG and JS: employees of and stockholders in AbbVie Biotherapeutics Inc.; WCB, PM and G Giannattasio: full-time employees of and stockholders in Biogen.

Acknowledgments

This study was sponsored by Biogen (Cambridge, MA, USA) and AbbVie Biotherapeutics Inc. (Redwood City, CA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Southport, CT, USA): funding was provided by Biogen and AbbVie Biotherapeutics Inc.

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