Effect of Anti-CD25 Antibody Daclizumab in the Inhibition of Inflammation and Stabilization of Disease Progression in Multiple Sclerosis

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Background: Several questions arise concerning the use of the anti-CD25 antibody daclizumab to treat multiple sclerosis (MS).

Objectives: To answer the following 3 questions related to the efficacy of daclizumab therapy in patients with MS: Is the therapeutic effect of daclizumab dependent on combination with interferon beta? Is a higher dosage of daclizumab more efficacious in patients with persistent disease activity? Can biomarkers predict full vs partial therapeutic response to daclizumab?

Design: An open-label baseline vs treatment phase II clinical trial of daclizumab in patients having MS with inadequate response to interferon beta. Three months of interferon beta treatment at baseline were followed by 5.5 months of interferon beta–daclizumab combination therapy. If patients experienced more than 75% reduction of contrast-enhancing lesions (CELs) on brain magnetic resonance imaging at month 5.5 compared with baseline, daclizumab was continued as monotherapy for 10 months. Otherwise, the dosage of daclizumab was doubled.

Setting: Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland.

Patients: Fifteen patients with MS receiving standard preparations of interferon beta who experienced more than 1 MS exacerbation or whose clinical disability increased in the preceding 12 months and who had at least 2 CELs on baseline brain magnetic resonance images.

Intervention: Daclizumab (1 mg/kg) as an intravenous infusion every 4 weeks in combination with interferon beta (months 0-5.5) and as monotherapy (months 6.5-15.5).

Main Outcome Measures: The primary outcome was the reduction of CELs among interferon beta monotherapy, interferon beta–daclizumab combination therapy, and daclizumab monotherapy. The secondary outcomes included immunologic biomarkers and changes in clinical disability.

Results: Overall, 5 of 15 patients (33%) experienced adverse effects of therapy. Two patients developed systemic adverse effects, and daclizumab therapy was discontinued. Although daclizumab monotherapy was efficacious in 9 of 13 patients with MS, interferon beta–daclizumab combination therapy was necessary to stabilize disease activity in the other 4 patients. Daclizumab therapy led to 72% inhibition of new CELs and significant improvement in clinical disability. Pilot biomarkers (increase in CD56bright natural killer cells and decrease in CD8 T cells) were identified that can differentiate between full and partial daclizumab responders.

Conclusions: Daclizumab monotherapy is effective in most patients who experienced persistent MS disease activity with interferon beta therapy. Interferon beta–daclizumab combination therapy or higher dosages of daclizumab may be necessary to achieve optimal therapeutic response in all patients. Biomarkers may identify patients with suboptimal response to daclizumab monotherapy. Administration among a large patient sample during a longer period is needed to fully define the safety and long-term efficacy of daclizumab as treatment for high-inflammatory MS.

Trial Registration: clinicaltrials.gov Identifier: NCT00001934


MULTIPLE SCLEROSIS (MS) is an immune-mediated disorder of the brain and spinal cord in which at least part of the inflammatory process can be objectively measured by contrast-enhancing lesions (CELs) on brain magnetic resonance (MR) imaging. When used as an add-on therapy to interferon beta, daclizumab significantly inhibits CELs in MS. Studies from our laboratory revealed an unexpected mechanism of action of daclizumab in MS—it increases the quantity and function of immunoregulatory CD56bright natural killer (NK) cells, which
Patients had sustained response to daclizumab (1 mg/kg) administered every 4 weeks blocks therapeutic efficacy in MS? In addition, although intravenous administration of methylprednisolone was disregarded and were treated with intravenous methylprednisolone sodium succinate (1 g/d for 5 days). Magnetic resonance images obtained within 28 days of intravenous administration of methylprednisolone were disregarded and were substituted by MR images from the following month. Four of 15 enrolled patients participated in a previously published short-term National Institutes of Health clinical trial of daclizumab plus interferon beta.1

**METHODS**

The trial design is shown in Figure 1. The trial was approved by the institutional review board. The inclusion criteria were as follows: age 18 to 65 years, relapsing-remitting or secondary progressive MS, Expanded Disability Status Scale (EDSS)3 score of 1.0 to 6.3, and suboptimal response to interferon beta (defined as >1 MS exacerbation or progression of sustained clinical disability by ≥1 EDSS step in the preceding 12 months). The presence of neutralizing antibodies to interferon beta was not assessed and did not represent an exclusion criterion. Patients with concurrent medical conditions that could affect the immune system or progression of disability were excluded from the study. Multiple sclerosis exacerbations were defined based on criteria by Schumacher et al2 and were treated with intravenous methylprednisolone sodium succinate (1 g/d for 5 days). Magnetic resonance images obtained within 28 days of intravenous administration of methylprednisolone were disregarded and were substituted by MR images from the following month. Four of 15 enrolled patients participated in a previously published short-term National Institutes of Health clinical trial of daclizumab plus interferon beta.1

**STUDY TREATMENT**

To be enrolled, patients had to have at least 0.67 new CELs per month on baseline MR images (Figure 1). Daclizumab (1 mg/kg) was administered as an intravenous infusion, initially 2 weeks apart for the first 2 doses and then every 4 weeks. After 7 doses of daclizumab (at month 5.5), the total number of CELs on a single MR image series was compared with the mean number of CELs during baseline. If more than 75% reduction of CELs was observed, interferon beta therapy was slowly withdrawn (during 2-4 weeks). If 75% or less reduction of CELs was observed at month 5.5, interferon beta therapy was continued, and the daclizumab dosage was increased to 2 mg/kg every 4 weeks. The quantity of CELs was analyzed monthly. If a sustained (>2-month) increase in CELs was noted with daclizumab monotherapy (above the mean with combination therapy), interferon beta therapy was reinstated, and the patient continued receiving interferon beta–daclizumab combination therapy until the end of the trial.

**Figure 1.** Trial design, patient enrollment, and outcomes. CELs indicates contrast-enhancing lesions; MR, magnetic resonance.

**Table 1.** Immunologic, MR Imaging, and Clinical Examination Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Immunologic Studies</th>
<th>MR Imaging and Clinical Examinations</th>
<th>Months on Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclizumab</td>
<td>x x x x</td>
<td>x x x x x x x x</td>
<td>0, 0.5, 1.5, 2.5, 3.5, 4.5, 5.5</td>
</tr>
<tr>
<td>Interferon Beta-Daclizumab Combination Therapy</td>
<td>x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x</td>
<td>6.5, 7.5, 8.5, 9.5, 10.5, 11.5, 12.5, 13.5, 14.5, 15.5</td>
</tr>
<tr>
<td>Interferon Beta</td>
<td>x x x x</td>
<td>x x x x</td>
<td>1-3</td>
</tr>
</tbody>
</table>

- **15 Patients were screened and fulfilled MR imaging criteria for enrollment (>0.67 CELs per image on baseline MR imaging).**
- **14 Patients fulfilled MR imaging criteria for withdrawal of interferon beta (>75% reduction of CELs at mo 5.5 compared with mean CELs at baseline).**
- **1 Patient did not fulfill criteria for interferon beta withdrawal, and daclizumab dosage was increased to 2 mg/kg.**
- **8 Patients had sustained response to daclizumab.**
- **2 Patients experienced adverse effects that required discontinuation of daclizumab.**
- **3 Patients fulfilled criteria for restarting interferon beta (>2 mo sustained increase in CELs above the mean during combination therapy).**
- **1 Patient finished interferon beta plus daclizumab 2 mg/kg.**

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To identify biomarkers that could predict full therapeutic response to daclizumab after withdrawal of interferon beta therapy, we defined partial responders to daclizumab monotherapy. These were patients who either required interferon beta–daclizumab combination therapy or experienced MS exacerbation, or those who had 50% or less reduction of CELs with daclizumab therapy.

OUTCOME MEASURES

The primary outcome measure was the reduction of new and total CELs from the baseline treatment period (interferon beta therapy), to the interferon beta–daclizumab combination therapy, and to the daclizumab monotherapy period. The secondary outcomes included the following: change in the volume of CELs, volume of T2-weighted lesions, volume of T1-weighted lesion hypointensities, brain atrophy (brain fractional volume), and change in clinical measures of disability. The change in clinical measures of disability was assessed by the following scores: EDSS11 (0 [normal] to 10 [death from MS]), Scripps Neurological Rating Scale13 (100 [normal] to 0 [death from MS]), and Multiple Sclerosis Functional Composite14 (MSFC [calculated as a z score based on all collective baseline data in the cohort; higher numbers indicate improvement of disability]).

IMMUNOLOGIC BIOMARKERS

Whole-blood samples were collected every 2 to 3 months and were processed within 1 hour of collection. Red blood cells were lysed by osmotic pressure, and white blood cells were stained using a panel of commercially available antibodies and analyzed by flow cytometry as previously described.1 Percentages of CD4+/CD3+ and CD8+/CD3+ T cells and CD56bright/CD56dim/CD3− NK cells were calculated for each time point. Absolute numbers of these cellular subpopulations were derived from the absolute lymphocyte count provided by the National Institutes of Health clinical center laboratory from identical sample collections.

MR IMAGING ANALYSIS

Magnetic resonance images were acquired at 1.5 T using a standard protocol.1 CELs were recorded on hard-copy films by consensus of 2 radiologists. All volumetric analyses were performed by a single experienced rater (T.H.) using semiautomated thresholding techniques (PV-WAVE13 and MEDx) as previously described.1

STATISTICAL ANALYSIS

Statistical differences between treatment periods were based on Friedman repeated-measures analysis of variance on ranks with predetermined P < .05, using the Newman-Keuls test to correct for multiple comparisons. Differences between full and partial responders were based on the Mann-Whitney rank sum test.

RESULTS

DEMOGRAPHICS AND SAFETY

The patient population is summarized in the Table. Two patients did not complete the trial because of adverse effects possibly related to daclizumab monotherapy. Both patients (patient 5 and patient 13) developed systemic immune responses 1 to 2 months after withdrawal of interferon beta therapy, characterized by mouth ulcers, photosensitivity rash, and transient formation of autoantibodies that required corticosteroid therapy for resolution. Two other patients developed adverse events that required transient cessation of daclizumab therapy because of lymphopenia (patient 6) and generalized lymphadenopathy (patient 7). Both patients received all subsequent courses of treatment with excellent outcomes. Patient 1 had a transient increase in bilirubin levels that did not necessitate discontinuation of daclizumab therapy.

EFFICACY

Patient 11 did not reach the interim end point of CEL reduction by more than 75% at month 5.5 and was given a double dose of daclizumab in addition to continuation of interferon beta therapy, with a subsequent excellent therapeutic response. In 14 patients, interferon beta was withdrawn after 5.5 months, but in 3 patients it was restarted because of sustained reappearance of CELs. Trial results (intent-to-treat analysis among all 15 patients) are shown in Figure 2. We observed 72% inhibition of new CELs (P < .002) and 77% inhibition of total CELs (P < .001) with daclizumab therapy. This inhibition of CELs developed gradually and continued during dosing so that the reduction in the volume of CELs reached statistical significance (P < .001) even when comparing combination therapy and monotherapy periods (Figure 2A). We observed improvements in all clinical measures of disability (P < .001 for the EDSS and Scripps Neurological Rating Scale and P = .002 for the MSFC) (Figure 2B). There were no significant changes in the volume of T2-weighted lesions (P = .42), while the volume of T1-weighted lesion hypointensities (P = .009) and the brain fractional volume (P < .001) increased transiently between baseline and combination therapy but stabilized between combination therapy and monotherapy (Figure 2C). The average/median whole-brain magnetization transfer ratio did not change significantly (P = .56) from baseline (0.334/0.340) to combination therapy (0.335/0.337) or monotherapy (0.336/0.339).

IMMUNOLOGIC STUDIES

It was previously reported that daclizumab therapy increases the number of CD56bright NK cells and that this increase in numbers correlates with the decrease in absolute numbers of peripheral CD4+ and CD8+ T cells.4 Results of this trial allowed us to answer the question whether this effect is related to interferon beta therapy. We observed a further increase in the number of CD56bright NK cells (P < .001) and a concomitant decrease in the absolute numbers of CD4+ (P = .008) and CD8+ (P = .002) T cells with daclizumab monotherapy compared with interferon beta–daclizumab combination therapy (Figure 3A). Based on the previous observation that CD56bright NK cells regulate T-cell responses,5 we assessed the ratios between CD56bright NK cells and effector lymphocyte subsets (Figure 3B), which also further decreased during daclizumab monotherapy (P < .001 for CD4+/CD56bright NK and CD8+/CD56bright NK cell ratios).

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Seven patients fulfilled criteria for partial responders to daclizumab monotherapy (see the “Methods” section and the Table). When analyzing immunologic differences between full and partial responders, full responders had at least a 10% decrease in CD8\(^+\) T cells and CD4\(^+\) T cells and at least a 300% increase in the number of CD56\(^{bright}\) NK cells during combination therapy compared with baseline (Figure 3C). Partial responders showed an increase or less than a 10% decrease in CD4\(^+\) T cells and CD8\(^+\) T cells and less than a 300% increase in the number of CD56\(^{bright}\) NK cells. Although full responders further increased the percentage of CD56\(^{bright}\) NK cells and CD8\(^{alpha}\)\(^{dim}/CD3\(^+\) lymphocytes during daclizumab monotherapy to more than 400% of baseline, partial responders experienced a significantly smaller increase in these regulatory cells (Figure 3C, last panel).

Our data demonstrate that while daclizumab monotherapy is effective for most patients with MS having persistent MR imaging and clinical evidence of disease activity while receiving interferon beta therapy, there is an additive effect of interferon beta–daclizumab combination therapy that may be advantageous for patients whose MS is most difficult to treat. Compared with a previous study by Rose et al\(^1\) that was performed concurrently with the initial daclizumab study at the Neuroimmunology Branch,\(^1\) the present study provides important additional information.

First, in addition to EDSS and Scripps Neurological Rating Scale clinical scores, which should be inter-

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>DD, y</th>
<th>MS Type</th>
<th>Interferon Beta-1b Therapy</th>
<th>Therapeutic Response</th>
<th>EDSS Score During Treatment Periods</th>
<th>Adverse Effects</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline (Last Visit Before Therapy)(^a)</td>
<td>Months 0-5.5 Mean</td>
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<td>1</td>
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<td>Betaseron</td>
<td>FR</td>
<td>2.0</td>
<td>2.4</td>
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<tr>
<td>2/F/29</td>
<td>3</td>
<td>RR</td>
<td>Avonex</td>
<td>FR</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>3/M/41</td>
<td>5</td>
<td>RR</td>
<td>Betaseron</td>
<td>PR (−5% overall inhibition of CELs)</td>
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<td>0.9</td>
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<tr>
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<td>RR</td>
<td>Betaseron</td>
<td>FR</td>
<td>2.0</td>
<td>1.7</td>
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<tr>
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<td>RR</td>
<td>Betaseron</td>
<td>FR (D/C during monotherapy at mo 7.5)</td>
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<td>0.8</td>
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<td>FR</td>
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<td>4.1</td>
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<td>SP</td>
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<td>FR</td>
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<td>8/M/19</td>
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<td>PR (MS exacerbation during therapy)</td>
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<td>1.7</td>
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<tr>
<td>9/F/35</td>
<td>7</td>
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<td>Betaseron</td>
<td>PR (MS exacerbation during therapy)</td>
<td>1.5</td>
<td>2.5</td>
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<td>10/F/46</td>
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<td>RR</td>
<td>Avonex</td>
<td>PR (restated interferon beta at mo 9.5 because of reappearance of CELs)</td>
<td>4.0</td>
<td>3.5</td>
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<td>11/M/44</td>
<td>16</td>
<td>SP</td>
<td>Betaseron</td>
<td>PR (received interferon beta plus daclizumab [2 mg/kg] during mo 6.5-15.5)</td>
<td>2.0</td>
<td>1.4</td>
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<tr>
<td>12/F/36</td>
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<td>RR</td>
<td>Betaseron</td>
<td>FR</td>
<td>2.0</td>
<td>1.7</td>
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<tr>
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<td>RR</td>
<td>Avonex</td>
<td>FR (D/C during monotherapy at mo 6.5)</td>
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<td>1.1</td>
</tr>
<tr>
<td>14/F/27</td>
<td>9</td>
<td>SP</td>
<td>Betaseron</td>
<td>PR (restated interferon beta at mo 12.5 because of reappearance of CELs)</td>
<td>5.5</td>
<td>4.6</td>
</tr>
<tr>
<td>15/F/39</td>
<td>7</td>
<td>RR</td>
<td>Rebif 44</td>
<td>PR (restated interferon beta at mo 9.5 because of reappearance of CELs)</td>
<td>6.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Abbreviations: CELs, contrast-enhancing lesions; D/C, discontinuation of therapy; DD, disease duration; FR, full responder; LFTs, liver function test results; MS, multiple sclerosis; PR, partial responder; RR, relapsing-remitting; SP, secondary progressive.

\(^a\)Because most patients were enrolled in proximity to multiple sclerosis exacerbation, we provide single Expanded Disability Status Scale (EDSS) scores just before initiation of daclizumab therapy to eliminate the influence of relapse-related disability. Baseline period means are shown in Figure 2A.

\(^b\)Patients who did not complete 15.5 months of daclizumab therapy.

**COMMENT**

Our data demonstrate that while daclizumab monotherapy is effective for most patients with MS having persistent MR imaging and clinical evidence of disease activity while receiving interferon beta therapy, there is an additive effect of interferon beta–daclizumab combination therapy that may be advantageous for patients whose MS is most difficult to treat. Compared with a previous study by Rose et al\(^1\) that was performed concurrently with the initial daclizumab study at the Neuroimmunology Branch,\(^1\) the present study provides important additional information.

First, in addition to EDSS and Scripps Neurological Rating Scale clinical scores, which should be inter-
preciated with caution in an open-label trial because of their
high rater dependency, we provide data on the MSFC,
which is based on objectively quantifiable measures.
Hence, the continuous improvement on the MSFC be-
tween combination therapy and monotherapy is encour-
aging. Although a learning effect may influence MSFC
scores when tested infrequently, all 3 components of the
MSFC were tested monthly in our trial, making it un-
likely that learning could have affected the results after
more than 10 months of testing.

Second, in addition to CEL analysis, our study evalu-
ates volumetric MR imaging measures, including magne-
tization transfer ratios. Although the improvement in dis-
ability measures suggests the possibility that daclizumab
therapy enhances repair, we consider this unlikely in view
of its apparent lack of effect on the volume of T1-
weighted lesion hypointensities and the brain fractional
volume. Nevertheless, these MR imaging measures may
detect edema associated with inflammation, which makes
them less sensitive markers for tissue destruction in short-
term clinical trials of MS.16 However, neither did we ob-
serve any improvement in whole-brain magnetization trans-
eration ratios, even though this too may be a measure that is
insensitive to depict focal lesion-related repair.

Third, our immunologic data demonstrated further in-
creases in CD56bright NK cells and additional decreases
in the number of CD4+ and CD8+ T cells after cessation
of interferon beta therapy. This indicates that interferon
beta and daclizumab have distinct immunologic mech-
nisms of action; therefore, their combination is more ef-
effective than either drug alone.

Fourth, although we treated only 1 patient with a higher
dosage of daclizumab (2 mg/kg), the remarkable efficacy
of this dosage (complete elimination of CELs in this pa-
tient for 10 months) suggests that higher dosages of da-
clizumab deserve further study as an alternative to inter-
feron beta–daclizumab combination therapy. Our obser-
vation of greater than 95% saturation of CD25 with
daclizumab on peripheral blood lymphocytes in all pa-
tients, irrespective of their response status (data not shown),
led us to believe that higher dosages of daclizumab may
be necessary to fully saturate CD25 in tissues.

Fifth, it would be of great benefit to have biomarkers
that allow prediction of treatment response. The results
of our study indicate that the extent of changes in CD8+
T-cell and CD56bright NK cell counts induced by dacli-
zumab within the first 2 to 4 months of therapy may iden-
tify patients who are unlikely to have a full therapeutic
response on withdrawal of interferon beta therapy. These
biomarker findings must be considered preliminary but
deserve validation in large phase II or III trials of dacli-
zumab. That we could demonstrate statistically signifi-
cant differences between full and partial responders even
in such a small cohort using nonparametric statistics is
encouraging.

The therapeutic efficacy of daclizumab in inhibiting brain
inflammation in MS has been confirmed by several trials,
including a recently reported randomized double-blind
phase II trial of interferon beta–daclizumab combina-
tion therapy (CHOICE [Daclizumab in Patients With Ac-
tive Relapsing-Remitting Multiple Sclerosis on Concur-
rent Interferon-Beta Therapy] study).17 This trial examined

Figure 2. Clinical and magnetic resonance (MR) imaging trial results. A, Effect
of daclizumab therapy on primary outcome measures, including the numbers
of new and total contrast-enhancing lesions (CEls) and the volume of CEls.
B, Effect of daclizumab therapy on secondary (clinical) outcome measures,
including scores on the Expanded Disability Status Scale (EDSS), Scripps
Neurological Rating Scale (NRS), and Multiple Sclerosis Functional Composite
(MSFC). C, Effect of daclizumab therapy on secondary (MR imaging) outcome
measures, including volume of T2-weighted lesions (T2L volume), volume of
T1-weighted lesions (T1L volume), and brain atrophy (brain fractional volume
(BFV)). For each patient, the means of the treatment periods are shown.
The medians of the whole cohort are bolded. ∗Statistically significant
differences (P < .05) between time points. Comb Th indicates combination
therapy; Mono Th, monotherapy; and ns, not significant.
Figure 3. Immunologic results. A, Changes in the subpopulations of CD56<sup>bright</sup> natural killer (NK) cells and CD8<sup>+</sup> and CD4<sup>+</sup> T cells during daclizumab (Dacliz) therapy. The medians of the whole cohort are bolded. Statistically significant differences (P < .05) between baseline, combination therapy, and monotherapy time points are indicated by horizontal bidirectional arrows (↔) in the graphs. B, The ratios of CD8<sup>+</sup> and CD4<sup>+</sup> T cells and CD56<sup>bright</sup> NK cells (responding populations) and CD56<sup>bright</sup> NK cells (regulatory population). Each patient point represents the mean of several treatment period time points (Figure 1). Statistically significant differences (P < .05) are indicated by an asterisk. C, Differences in immunologic markers between 8 full responders (FR) and 7 partial responders (PR) to daclizumab monotherapy (Table). Individualized percentage changes in biomarkers compared with baseline were calculated for all patients and are depicted as box plots. Black horizontal line represents median; white horizontal line, group mean; blue dashed line, baseline (100%) values. Comb Th indicates combination therapy; Mono Th, monotherapy.
the efficacy of a formulation for subcutaneous delivery of 2 dosages of daclizumab (1 mg/kg and 2 mg/kg) administered every 2 weeks vs placebo. The study patients who received the higher dosage had a statistically significant 72% reduction in the number of new or enlarged CELs at week 24 compared with patients receiving interferon beta therapy alone. Other phase II trials, including those testing the efficacy of daclizumab monotherapy, are ongoing. However, daclizumab must undergo rigorous testing in phase III double-blind clinical trials before it can be considered a safe and effective therapy for patients with MS.

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