ABSTRACT

Objective: To characterize the reversibility of natalizumab-mediated changes in pharmacokinetics/pharmacodynamics in patients with multiple sclerosis (MS) following therapy interruption.

Methods: Pharmacokinetic/pharmacodynamic data were collected in the Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis (AFFIRM) (every 12 weeks for 116 weeks) and Randomized Treatment Interruption of Natalizumab (RESTORE) (every 4 weeks for 28 weeks) studies. Serum natalizumab and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured using immunoassays. Lymphocyte subsets, α4-integrin expression/saturation, and vascular cell adhesion molecule-1 (VCAM-1) binding were assessed using flow cytometry.

Results: Blood lymphocyte counts (cells/L) in natalizumab-treated patients increased from 2.1 × 10^9 to 3.5 × 10^9. Starting 8 weeks post last natalizumab dose, lymphocyte counts became significantly lower in patients interrupting treatment than in those continuing treatment (3.1 × 10^9 vs 3.5 × 10^9; p = 0.031), plateauing at prenatalizumab levels from week 16 onward. All measured cell subpopulation, α4-integrin expression/saturation, and sVCAM changes demonstrated similar reversibility. Lymphocyte counts remained within the normal range. Ex vivo VCAM-1 binding to lymphocytes increased until ≈16 weeks after the last natalizumab dose, then plateaued, suggesting reversibility of immune cell functionality. The temporal appearance of gadolinium-enhancing lesions was consistent with pharmacodynamic marker reversal.

Conclusions: Natalizumab’s effects on peripheral immune cells and pharmacodynamic markers were reversible, with changes starting 8 weeks post last natalizumab dose; levels returned to those observed/expected in untreated patients by 16 weeks post last dose. This reversibility differentiates natalizumab from MS treatments that require longer reconstitution times. Characterization of the time course of natalizumab’s biological effects may help clinicians make treatment sequencing decisions.

Classification of evidence: This study provides Class III evidence that the pharmacodynamic markers of natalizumab are reversed ≈16 weeks after stopping natalizumab. Neurology® 2017;89:1584–1593

GLOSSARY

AFFIRM = Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis; CTS = Clinical Trials Services; EID = extended interval dosing; Gd+ = gadolinium-enhancing; MS = multiple sclerosis; NK = natural killer; PD = pharmacodynamics; PK = pharmacokinetics; RESTORE = Randomized Treatment Interruption of Natalizumab; RRMS = relapsing-remitting multiple sclerosis; sVCAM-1 = soluble vascular cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; WBC = white blood cell.

A number of therapies for relapsing-remitting multiple sclerosis (RRMS) are currently available; each has a distinct mechanism of action and benefit/risk profile and exhibits a different temporal pattern with respect to reversibility of the drug’s overall biological effects. Given the expansive and complex RRMS treatment landscape, when patients experience treatment failure and
alternative therapies are being considered, treatment sequencing is an important issue. Understanding the temporal nature of the biological effect of individual therapies may facilitate treatment selection.

Natalizumab is a recombinant humanized monoclonal antibody that targets the α4 subunit of the α4β1 integrin on mononuclear leukocytes and is approved for the treatment of relapsing multiple sclerosis (MS). When bound by natalizumab, α4β1 integrin is blocked from binding to vascular cell adhesion molecule-1 (VCAM-1), disrupting the homing and trafficking of mononuclear leukocytes across activated vascular endothelium of the CNS.

The pharmacodynamics (PD), the drug effect on biological systems, of natalizumab include increased saturation/occupancy by natalizumab of its target, α4-integrin (CD49d), on the surface of circulating lymphocytes, decreased surface expression of α4-integrin on lymphocytes; and decreased serum concentration of soluble VCAM-1 (sVCAM-1). Natalizumab use is also associated with increased levels of peripheral immune cells, although these levels remain within the normal range for all investigated cell types except CD34+ progenitor cells.

Natalizumab is highly efficacious at reducing both clinical and radiologic disease activity. Upon natalizumab treatment interruption, disease activity returns, with the earliest MRI lesions observed 12 weeks after the last natalizumab dose. However, the time course of reversibility of natalizumab’s effects on immune cells is not well-characterized. Data from 2 large clinical trials allowed assessment of changes that occur upon natalizumab initiation (Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis [AFFIRM] study) and following the last natalizumab dose (Randomized Treatment Interruption of Natalizumab [RESTORE] study). We analyze the pharmacokinetics (PK), the time course of drug concentration, and the PD from these studies to further characterize the timing of the biological changes in the peripheral compartment associated with natalizumab treatment initiation and interruption.

METHODS Study design. AFFIRM was a randomized, multicenter, double-blind, placebo-controlled phase 3 trial conducted from November 2001 to January 2005 (NCT00027300; clinicaltrials.gov). Details of the study design and patient population were previously published. Patients were randomized 2:1 to receive 300 mg natalizumab or placebo IV every 4 weeks for up to 116 weeks.

RESTORE was a randomized, multicenter, partially blinded, parallel-group exploratory study conducted between March 2010 and November 2011 (NCT01071083; clinicaltrials.gov). Details of the study design and patient population were previously published. Patients who had received 300 mg natalizumab IV for ≥12 months prior to trial entry were randomized (1:1:2) to natalizumab, placebo, or alternate therapy (IM interferon-β-1a [Avonex; Biogen, Cambridge, MA], glatiramer acetate [Copaxone; Teva Neuroscience, Kansas City, MO], or methylprednisolone). Administration of natalizumab and placebo was double-blind; alternative therapies were administered open-label. Randomization occurred at week 0 (in which all patients received their last natalizumab infusion). At week 28, patients discontinued placebo or alternate therapy and restarted open-label natalizumab, which patients who experienced 1 new gadolinium-enhancing (Gd+) lesion of ≥0.8 cm³ in volume, ≥2 Gd+ lesions of any size, or ≥1 clinical relapses could receive high-dose corticosteroid treatment or restart open-label natalizumab treatment at the investigator’s discretion. Patients who received open-label natalizumab during the treatment interruption period proceeded directly to the open-label follow-up period.

Primary research question. This analysis was conducted to characterize the timing of the PK and PD changes, including changes in peripheral immune cells, upon natalizumab treatment initiation and interruption.

Classification of evidence. This study provides Class III evidence that the PD markers of natalizumab’s activity are reversed ≥16 weeks after stopping natalizumab.

Assessments. In AFFIRM, samples for PK and limited PD evaluations (total lymphocyte and white blood cell [WBC] counts) were taken from all patients at baseline (prenatalizumab) and prior to infusion at weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120. A cohort of 31 patients (natalizumab, n = 50; placebo, n = 11) from a subset of US sites underwent weekly measurement of α4-integrin saturation following the first dose of natalizumab; α4-integrin saturation was also measured every 24 weeks in a separate subset of 21 patients (natalizumab, n = 15; placebo, n = 6). Blood for hematology and serum chemistry were analyzed at a central laboratory (Covance Central Laboratory Services, Indianapolis, IN; Covance, Geneva, Switzerland; or Sonic Trials Laboratory, North Ryde, Australia). Natalizumab concentration was measured by Biogen using an ELISA; α4-integrin saturation on circulating lymphocytes (indicating the proportion of α4-integrin receptors on the lymphocyte cell surface membrane occupied by natalizumab) was analyzed using flow cytometry by Elan Pharmaceuticals (Dublin, Ireland). The normal range for peripheral blood cells was defined as the normal range in healthy individuals as provided by Covance (shown in table e-1 at Neurology.org).

In RESTORE, clinical, MRI, and laboratory evaluations were performed at baseline and weeks 4, 8, 12, 16, 20, 24, and 28 of the randomized treatment period. Serum natalizumab concentration was measured at Charles River Laboratories Preclinical Services (Senneville, Canada). Serum VCAM-1 concentration was measured using a LINCOplex immunoassay (Lincos Research, Inc.; St. Charles, MO) at Covance (Geneva, Switzerland, and Indianapolis, IN). In addition to the cell subsets analyzed in AFFIRM, the following lymphocyte populations were analyzed: CD3+CD4+ T cells, CD3+CD8+ T cells, CD19+ B cells,
natural killer (NK) cells (CD3−/CD16+CD56+), and hematopoietic stem cells (CD34+/CD45+). Lymphocyte and leucocyte subset counts, CD4 integrin saturation, CD49d expression, and binding of cells to fluorescently labeled VCAM-1–immunoglobulin reagent were determined using flow cytometric analysis of whole blood by Esoterix Clinical Trials Services (CTS–Belgium (Mechelen, Belgium) or Esoterix CTS–Cranford (Cranford, NJ), except for lymphocyte–VCAM-1 binding assays, which were performed by Esoterix CTS–Cranford. Flow cytometry reagents and gating strategies are shown in appendix e-1. Because the prenatalizumab levels for lymphocyte subsets were not measured in RESTORE, values were compared with normal ranges reported in the literature.11,14

Standard protocol approvals, registration, and patient consent. For both the AFFIRM and RESTORE studies, the protocol was reviewed and approved by site institutional review boards. All patients provided written informed consent, and the studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines on Good Clinical Practice.

Statistical analyses. RESTORE participants were categorized into 2 groups: those who continued natalizumab treatment and those whose natalizumab treatment was interrupted (i.e., switched from natalizumab to placebo or an alternative therapy). Combining the patients who switched from natalizumab into a single group provided additional statistical power to examine differences between those who remained on natalizumab and those who interrupted natalizumab treatment. Repeated-measure models were employed to calculate statistical differences in PK and PD over time between the 2 groups. Estimates were obtained for each treatment group from all available data at each collection time.

Table 1 Baseline characteristics of RESTORE patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Natalizumab treatment continued (n = 45)</th>
<th>Natalizumab treatment interrupted (n = 130)</th>
<th>Total (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>41.2 (9.70)</td>
<td>41.2 (9.94)</td>
<td>41.2 (9.85)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>37 (82)</td>
<td>98 (75)</td>
<td>135 (77)</td>
</tr>
<tr>
<td>Time since MS symptom onset, y</td>
<td>[2–40]</td>
<td>[2–41]</td>
<td>[2–41]</td>
</tr>
<tr>
<td>EdSS score at randomization</td>
<td>[1.75]</td>
<td>[1.72]</td>
<td>[1.73]</td>
</tr>
<tr>
<td>Median (range)</td>
<td>[0–6.5]</td>
<td>[0–8.0]</td>
<td>[0–8.0]</td>
</tr>
<tr>
<td>Total number of natalizumab infusions prior to randomization</td>
<td>[10.88]</td>
<td>[9.73]</td>
<td>[10.01]</td>
</tr>
<tr>
<td>Median (range)</td>
<td>[12, 49]</td>
<td>[12, 51]</td>
<td>[12, 51]</td>
</tr>
</tbody>
</table>

Abbreviations: EdSS = Expanded Disability Status Scale; MS = multiple sclerosis; RESTORE = Randomized Treatment Interruption of Natalizumab.* No. = 129.
Peripheral blood cell counts. In AFFIRM, total lymphocyte counts at baseline were the same in the natalizumab and placebo groups. While minimal change was observed in placebo-treated patients during the study, the least-squares mean estimate of total blood lymphocytes in natalizumab patients increased from $2.1 \times 10^9$ cells/L at baseline to $3.5 \times 10^9$ cells/L at week 12, the first evaluated time point. These levels reached a plateau of $3.7 \times 10^9$ cells/L 24 weeks after natalizumab initiation and stayed in the $3.5 \times 10^9$–$3.7 \times 10^9$ cells/L range for the remainder of the study (figure e-1C).

Levels of other peripheral blood cells were also analyzed in AFFIRM. Natalizumab treatment was associated with increases in total leukocyte (WBC), monocyte, basophil, and eosinophil counts over 120 weeks, similar to the increase in total lymphocyte count (figure e-1, D–G). Neutrophils, the only major leukocyte class with very low α4-integrin expression, showed no significant difference in cell counts between natalizumab- and placebo-treated patients (figure e-1H). For all measured peripheral blood cells, mean counts remained within the normal range throughout the study period.

PK/PD after natalizumab treatment interruption in RESTORE. Serum natalizumab. In RESTORE, natalizumab concentrations at baseline and week 4 were similar in patients continuing natalizumab and those whose treatment was interrupted (30.6 vs 32.9 μg/mL for week 0; figure 1A). At week 8, natalizumab levels were significantly lower in patients who had interrupted treatment than in those who continued natalizumab (8.7 vs 34.7 μg/mL; p < 0.001). Starting at week 16, natalizumab concentrations were below the lower limit of quantification (0.25 μg/mL) for >33% of the patients who had interrupted treatment; therefore, mean natalizumab levels were not calculated for this cohort from week 16 onward.

α4-Integrin saturation and other PD markers. RESTORE patients had been treated with natalizumab for >1 year prior to study entry. Accordingly, their mean trough α4-integrin saturation levels at baseline (86%) (figure 1B) were similar to the levels observed in natalizumab-treated patients in AFFIRM (figure e-1B). RESTORE patients who continued natalizumab consistently maintained mean trough α4-integrin saturation levels near 85%–90%. At week 8, saturation levels were significantly lower in patients who had stopped natalizumab than in those who were maintained on treatment (68% vs 87%; p < 0.001); saturation levels in patients with natalizumab treatment interruption continued to decline at week 12 and reached a plateau of approximately 10%–15% saturation (consistent with values observed prior to natalizumab treatment in AFFIRM) by about week 16.

In patients whose natalizumab treatment was interrupted, serum sVCAM concentration and α4-integrin (CD49d) expression each increased from baseline levels starting at week 8 and reached plateaus at approximately week 16, concurrently with decreases in natalizumab concentration and α4-integrin saturation (figure 1, C and D).

Peripheral blood cell counts. Among RESTORE patients who continued natalizumab treatment, absolute lymphocytes and lymphocyte subset cell counts did not change significantly during the randomized treatment period (figure 2, A–F). In contrast, patients who stopped natalizumab showed a significant reduction in total lymphocyte counts starting 8 weeks after the last natalizumab dose compared with patients continuing natalizumab (3.1 × 10^9 cells/L vs 3.5 × 10^9 cells/L; p = 0.031; figure 2A). From 16 weeks onward, total lymphocyte counts in patients who discontinued natalizumab treatment remained below those of patients who continued natalizumab (1.9 × 10^9 cells/L vs 3.4 × 10^9 cells/L; p < 0.001) and plateaued at levels similar to those observed prior to natalizumab initiation (2.1 × 10^9 cells/L, as assessed in AFFIRM prior to natalizumab treatment; figure e-1C). Similar trends were observed regardless of whether patients switched to placebo, interferon-β-1a, glatiramer acetate, or methylprednisolone (figure e-2).

All measured lymphocyte subpopulations whose levels were affected by natalizumab, including T, B, and NK cells, as well as CD34+ hematopoietic progenitor cells, demonstrated similar time courses of reversibility after the last natalizumab dose (figure 2, B–F). Compared with leukocyte levels in patients who continued natalizumab, patients whose treatment was interrupted exhibited significant decreases from baseline in total WBC, monocyte, basophil, and eosinophil counts at week 16 (p < 0.001; figure e-3, A–D). No notable change in cell counts or difference between the on-natalizumab and natalizumab-interruption groups was observed for neutrophils (figure e-3E).

Subgroup analyses. When RESTORE patients were grouped based on age, younger patients (≤42 years) tended to have higher total lymphocyte counts than older patients (>42 years) throughout the study (figure 2G). Similarly, total lymphocyte counts were higher in patients with high vs low disease activity (figure 2H) and in women vs men (figure 2I). In each of these subgroups, the temporal profile of reversibility was comparable to that observed in the overall population, with significantly lower levels observed starting at week 12 in all patient groups with natalizumab treatment.
interruption than in those who continued treatment. Total lymphocyte counts plateaued at week 16 and were maintained at levels similar to those observed prior to natalizumab (as assessed in the AFFIRM natalizumab arm; figure e-1C).

Functional assays. T cells, B cells, and monocytes from patients whose treatment was interrupted demonstrated significantly greater ex vivo binding to VCAM-1 starting at week 12 (p < 0.001 for B cells and monocytes; p = 0.001 for T cells) than in patients who remained on natalizumab (figure 3). VCAM-1 binding progressively increased through approximately 16 weeks after the last natalizumab dose and then plateaued.

Return of disease activity. When α4-integrin saturation values were evaluated in relation to the timing of the appearance of Gd+ lesions in the overall population of RESTORE, a temporal relationship was observed between decreases in α4-integrin saturation and the appearance of Gd+ lesions (figure 4).

DISCUSSION Given the growing number of available disease-modifying therapies for RRMS, treatment sequencing decisions are becoming more complex and require careful considerations of the mechanism of action, safety, efficacy, and reversibility of each drug’s effects. Using data from the RESTORE study, we provide a comprehensive evaluation of the
reversibility of natalizumab's PK and PD effects and their relationship to clinical and MRI characteristics. The pattern of reversibility demonstrated here adds to previous analyses to offer a more complete profile of the temporal effects of natalizumab discontinuation. The earliest detectable changes in PK and PD markers were observed 8 weeks after natalizumab treatment interruption and involved serum natalizumab concentration and α4-integrin saturation on peripheral lymphocytes. By week 12, peripheral lymphocyte subset counts had decreased significantly, and by week 16 all PK and PD markers appeared similar to those observed in patients not treated with natalizumab. This reversal of natalizumab's PK and PD effect coincided with the return of clinical and radiologic disease activity. Gd+ lesions were observed in RESTORE as early as 12 weeks after the last dose of natalizumab, with the majority of Gd+ lesions appearing at and after 16 weeks following natalizumab discontinuation, suggesting that the PD and pharmacologic effects of natalizumab are tightly linked.

As some MS therapies are known to affect immune cell composition, we assessed change in total lymphocyte counts in groups stratified by demographics and disease activity. Least squares (LS) mean estimates ± 95% confidence interval (CI) are shown for patients continuing and discontinuing natalizumab classified by (G) age, (H) disease activity, and (I) sex. The arrow represents the last dose before the 24-week interruption period. The shaded area shows the range of normal lymphocyte counts (total lymphocyte counts: 0.91–4.28 × 10^9 cells/L [Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis (AFFIRM); CD4+ T cells14: 491–2,000 cells/mm^3; CD8+ T cells14: 314–2,087 cells/mm^3; CD19+ B cells14: 64–800 cells/mm^3; CD3−/CD16−/CD56− NK cells14: 27–693 cells/mm^3; CD34−/CD45+ hematopoietic progenitor cells15: 1.4–2.2 cells/mm^3]. For total lymphocytes (A, G, H, I), the gray dashed line indicates total lymphocyte counts prior to natalizumab treatment in the AFFIRM natalizumab treatment arm (2.08 × 10^9 cells/L), as shown in figure e-1C. Lymphocyte subsets were not assessed in AFFIRM. RESTORE = Randomized Treatment Interruption of Natalizumab.

*p < 0.05. **p < 0.001.
For a comprehensive understanding of natalizumab’s biological effects, and to establish comparator PK/PD marker levels for patients without natalizumab treatment, the present analyses employed data from the AFFIRM study. Although these findings from AFFIRM have previously been mentioned, this report serves as the first presentation of those data.

As previously reported, treatment with natalizumab is associated with increases in circulating immune cells from prenatalizumab levels, although these levels remain within the normal range. The magnitude and timing of the changes observed in natalizumab-treated patients were similar to those published in smaller observational studies. CD34+ hematopoietic progenitor cells were previously found to increase above the normal reference levels in natalizumab-treated patients. We observed similarly increased levels of CD34+ cells (mean of 7.7 cells/mm³); however, clonality (evaluated by the excess immunoglobulin light chain kappa or lambda proteins on cells) was not observed (data not shown), and counts returned to the normal range approximately 16 weeks after treatment interruption.

Increases in activated T cells expressing proinflammatory cytokines were also reported for natalizumab-treated patients; however, this study did not assess cytokine production.

A key limitation of the present analyses is that RESTORE patients were already receiving natalizumab at the start of the study; therefore, prenatalizumab levels

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**Figure 3** Functional activity of CD3+ T cells, CD19+ B cells, and monocytes from RESTORE patients

![Graph showing functional activity of CD3+ T cells, CD19+ B cells, and monocytes from RESTORE patients.](image)

Least squares mean estimates ± 95% confidence interval are shown for ex vivo binding of cells to vascular cell adhesion molecule-1 (VCAM-1). The arrow represents the last dose before the 24-week interruption period. MESF = molecules of equivalent soluble fluorochrome; RESTORE = Randomized Treatment Interruption of Natalizumab. *p = 0.001 for T cells; **p < 0.001 for T cells, B cells, and monocytes.

**Figure 4** Relationship of α4-integrin saturation and the incidence of gadolinium-enhancing (Gd+) lesions over time after the last natalizumab dose

![Graph showing relationship between α4-integrin saturation and Gd+ lesion incidence.](image)

The median α4-integrin saturation level and the cumulative percentage of patients with a natalizumab treatment interruption developing Gd+ lesions are shown. The last natalizumab dose was administered on day 0. Patients with >1 Gd+ lesion, %, represents the cumulative percentage of study patients with Gd+ lesions out of all patients not treated with natalizumab who remained in the study at that time point.
were not available for this population. Some assessments were performed at baseline in AFFIRM, yielding data that served as surrogate prenatalizumab reference levels. However, not all of the cell types assessed in RESTORE were measured in AFFIRM, and the baseline characteristics of AFFIRM and RESTORE patients were somewhat different. Specifically, AFFIRM patients were younger and had been diagnosed with MS more recently than RESTORE patients. Thus, PK and PD responses might differ between the AFFIRM and RESTORE patients. Indeed, characteristics such as age, race, and disease severity may influence circulating lymphocyte counts.\textsuperscript{31,32} Similarly, in a sub-analysis of RESTORE patients, those who were younger and those with high disease activity had higher total lymphocyte counts than older patients or those with lower disease activity. Nevertheless, the reversibility of CSF lymphocyte changes was not assessed in RESTORE. Findings from a previous study by Stüve et al.\textsuperscript{35} suggest that the effects of natalizumab on CSF lymphocyte counts may persist as long as 6 months after treatment cessation. How-ever, the observations of that study may be limited by the small sample size, the lack of prenatalizumab CSF data, and the use of nonrandomized controls.

Overall, the results of this study demonstrate that the PD effects of natalizumab on peripheral immune cells and other markers begin to decline starting at weeks 8–12, with levels returning to those observed or expected for patients not treated with natalizumab around 16 weeks after the last natalizumab dose. The reversal of PD changes was tightly linked with the recurrence of disease activity measured by MRI. A thorough understanding of a drug’s reversibility can inform the timing of initiation of an alternative therapy. Immuno-therapies available or soon to be available for MS treatment such as alemtuzumab, ocrelizumab, and cladribine, whose mechanisms of action rely on depletion of specific cell populations, appear to require at least 9–18 months, and possibly up to 35 months, to reconstitute the depleted B- and T-cell populations.\textsuperscript{17–21} Given the complexity of RRMS treatment options, the qualitative and quantitative characterization of the biological effects of natalizumab reported here may help clinicians make treatment-sequencing decisions.
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REFERENCES


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Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients
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This information is current as of September 15, 2017
CORRECTION

Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients

In the article “Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients” by Plavina et al., there is an error in the “Monocyte/VCAM-1 binding” key of figure 3. “Natalizumab continued” should have been represented by a green line and gray square; “Natalizumab interrupted” should have been represented by a red line and black circle. The editorial office regrets the errors.

Figure 3 Functional activity of CD3+ T cells, CD19+ B cells, and monocytes from RESTORE patients

Reference