A Comparative Analysis of Lymphocyte Subpopulations in Patients on Natalizumab, Fingolimod, and Dimethyl Fumarate

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Introduction
The impact of multiple sclerosis therapeutics on specific cell lines may inform understanding of risk as well as possible response to drug. The oral disease modifying therapies dimethyl fumarate (DMF) and fingolimod are known to decrease lymphocyte counts and, like natalizumab, have been associated with risk of infectious complications (most notably progressive multifocal leukoencephalopathy or PML).

With regard to dimethyl fumarate, clinical trials noted that approximately 5-6% of patients develop severe lymphopenia (ALC <500 cells/µl) over an average of 9 months and profound lymphopenia is cautioned against. Particular risk factors in developing lymphopenia include patient age >60, absolute lymphocyte counts < 2.0, higher EDSS, and pre-DMF interferon use.2,4 Interestingly, DMF-induced lymphopenia has been noted to cause a more dramatic reduction in CD8+ counts, which may be linked with PML.9

With regard to fingolimod, it has been noted that lymphocyte subpopulations, particularly those in the setting of natalizumab discontinuation, a low CD4+/CD8+ ratio has also been reported to confer higher risk of disease reactivation.9 Several studies have shown that natalizumab decreases CD4+ more than CD8+ T cells interestingly, in the setting of natalizumab discontinuation, a low CD4+/CD8+ ratio has also been reported to confer higher risk of disease reactivation.6

We sought to further investigate how these therapies affect lymphocyte subpopulations, noting that this information may have relevance to understanding disease course or risk and could potentially impact drug sequencing.

Methods
Chart review of over 500 patients was performed. Selection criteria included a diagnosis of MS, 3-month duration on the therapy, and at least one immunologic profile. This analysis yielded 76 patients. Further stratified by therapy used, this yielded 56 patients treated with either natalizumab, fingolimod, or dimethyl fumarate. Data were examined retrospectively.

Results

- Lymphocyte subsets in patients taking natalizumab were significantly higher.
- CD8+.
- Dimethyl fumarate (DMF) and fingolimod had substantial effects on the three cell lines studied when compared to natalizumab.

<table>
<thead>
<tr>
<th>Lymphocyte Subpopulations</th>
<th>Natalizumab</th>
<th>DMF</th>
<th>Fingolimod</th>
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<tbody>
<tr>
<td>CD3 (µ)</td>
<td>1680</td>
<td>1090**</td>
<td>462**</td>
</tr>
<tr>
<td>CD4 (µ)</td>
<td>1115</td>
<td>780**</td>
<td>264***</td>
</tr>
<tr>
<td>CD8 (µ)</td>
<td>517</td>
<td>269**</td>
<td>134***</td>
</tr>
</tbody>
</table>

Values above are in cells/mm³

- Fingolimod also lowered CD4+ and CD8+ significantly more than DMF

Lastly, a differential effect was noted:
- CD8 cells were more affected by DMF than CD4 or CD3 cells
- CD4 cells were more affected by Fingolimod than CD8 or CD3 cells

Because the CD8+ decrease for DMF was proportionally greater than its impact on CD4+, CD4+/CD8+ ratios were increased (µ: 3.89).
The reverse was true for fingolimod; and, though ratios remained in normal range (indicated by bars above), CD4+/CD8+ ratios were decreased (µ: 1.43).

This trend upheld over time where data was available (25 patients total with longitudinal data, 2 on natalizumab, 20 on DMF and 3 on fingolimod): Changes in CD4+/CD8+ ratio over time on different therapies

Conclusions
Given potential concerns about safety and what lymphocyte counts may tell us about treatment response, we believe the differential effects on cell types observed with these therapies may be important to understand.

Our data reveal both the impact and nature of the changes that therapies have on lymphocyte subtypes and ratios.
- Significant decreases were observed in all three cell lines studied in patients on dimethyl fumarate and fingolimod when compared to natalizumab
- DMF increased CD4+/CD8+ ratios, while fingolimod decreased such ratios

Limitations of this study include:
- Retrospective design, with lack of [untreated] control group or baseline values
- Immunologic profiles were not performed consistently or in all patients on these therapies at our site, limiting the cohort
- Extended monitoring is lacking in some cases.

Future Directions
The impact of these medications on lymphocyte subpopulations may become more clinically relevant as we come to better understand the relationship of infectious complications and/or treatment response to said counts.

Patients may change therapies and it may become important to know what to expect in lymphocyte profiling as they switch drugs.

Further study may support a role for initial and interval monitoring of lymphocyte subpopulations in MS patients on disease-modifying therapies.

We would like to understand what happens over longer periods of time and how these changes may be important to understand.

References

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