

Leprosy in Two Patients with Relapsing Remitting Multiple Sclerosis Treated with Fingolimod

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Background

Leprosy (Hansen's disease) is a chronic infection caused by *Mycobacterium leprae*. The disease develops over months to years and may cause extensive damage to the skin and peripheral nervous system.

In multiple sclerosis (MS), fingolimod treatment is known to increase the risk for infections. There is one prior reported case of leprosy while on fingolimod for relapsing remitting multiple sclerosis (RRMS). We report two further cases of leprosy in patients with RRMS and treated with fingolimod.

Methods

Retrospective chart review of patient records of individuals with MS treated with fingolimod, followed at the Maxine Mesinger Multiple Sclerosis Clinic at Baylor College of Medicine.

Results

Two female patients [63 (P1) and 71 (P2) years old] with a diagnosis of leprosy were identified.

The diagnosis was made via skin biopsy and the mean time of diagnosis from the initiation of fingolimod was 34.5 months.

P1's absolute lymphocyte count (ALC) was 451 seven months prior to the diagnosis. P2's ALC was 118 two months prior to the diagnosis.

Both patients were potentially exposed to armadillo feces.



Figure 1. [A] Feet deformity, [B] nodular skin lesion, [C] foot edema, and [D] joint swelling in P2.

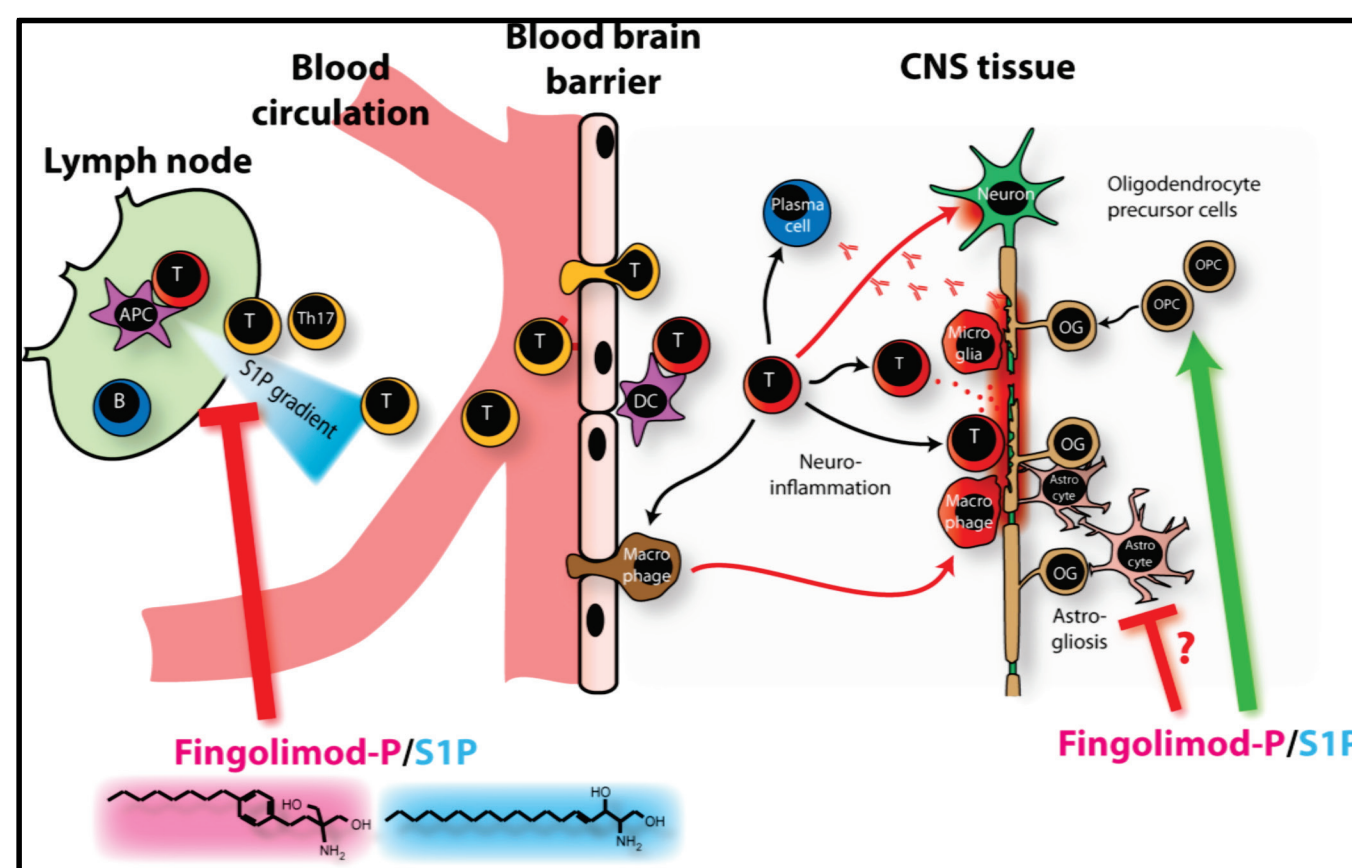


Figure 2. Fingolimod-Mechanism of Action: Fingolimod is a sphingosine-1-phosphate partial agonist, which in turn down regulates sphingosine-1-phosphate receptors on cells, resulting in the sequestration of lymphocytes in lymph nodes. Immuno-suppression via drug-induced lymphopenia is a known adverse side effect and is closely monitored for while taking fingolimod.

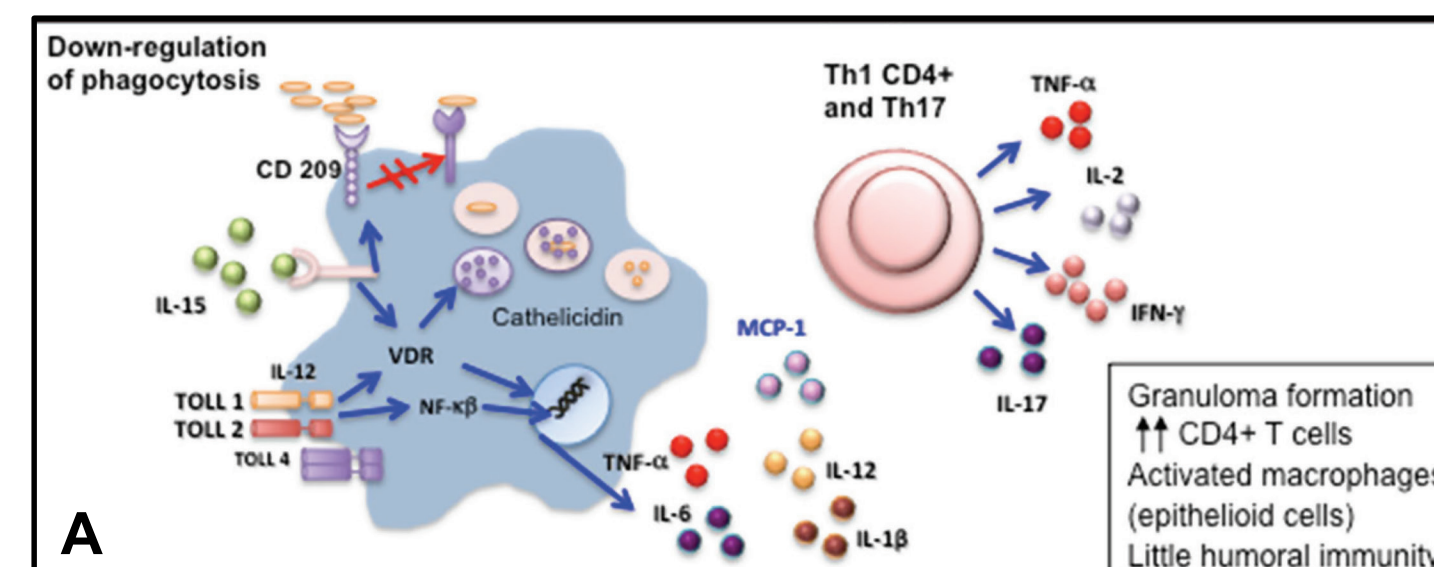
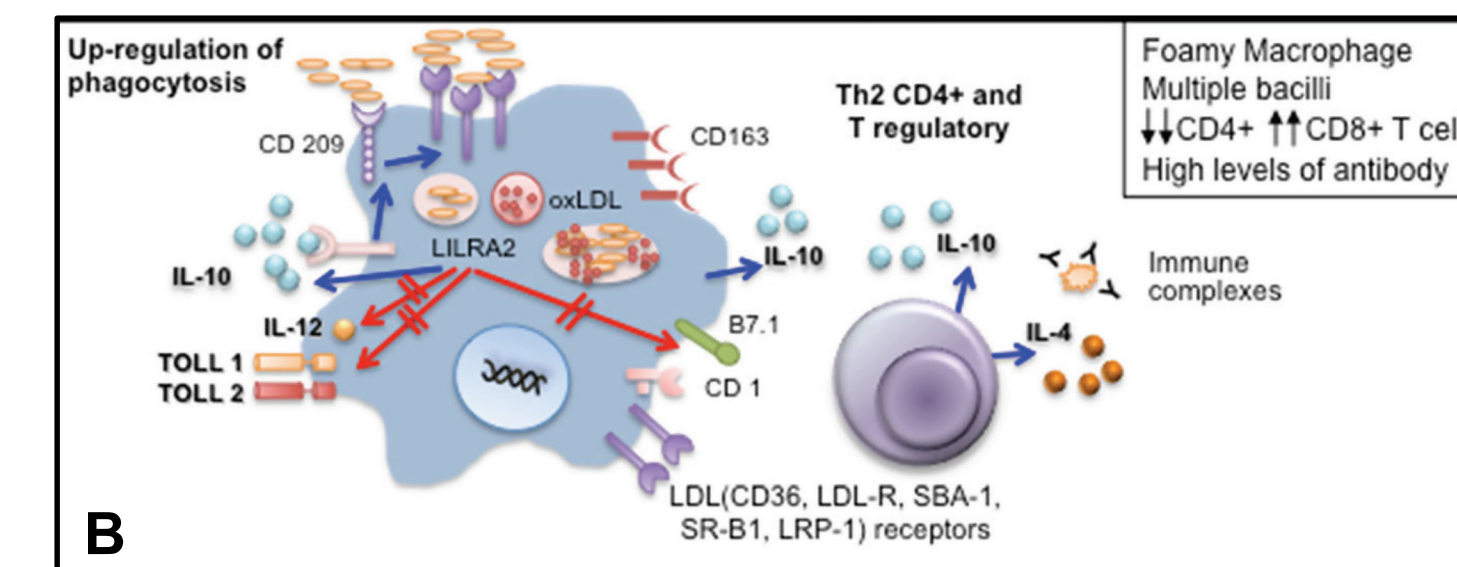


Figure 3. Immune response in the polar clinical forms of leprosy.

[A] In tuberculoid leprosy (TT) patients, the innate immune response is activated by *M. leprae* through toll-like receptors (TLR2/1). IL-15 stimulates the vitamin D-dependent antimicrobial program in macrophages and inhibits phagocytosis of mycobacteria. These events promote a Th1 T-cell cytokine response (IFN- γ , IL-2, TNF, and IL-15) that contains the infection in well-formed granulomas, and a Th17 response (IL-17A, IL-17F, IL-21 and IL-22) that leads to tissue inflammation and destruction, neutrophil recruitment, macrophage activation, and enhancement of Th1 effector cells.

[B] In lepromatous leprosy (LL) patients, IL-4, IL-10, leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2), and oxidized phospholipids inhibit TLR2/1-induced cytokine responses but preserve IL-10 release. In addition, immune complexes trigger IL-10 production and increase phagocytosis of *M. leprae*, ApoB, haptoglobin-hemoglobin complex and oxidized phospholipids by macrophages through the receptors CD209 and CD163, without activating the vitamin D-dependent antimicrobial pathway. The foamy appearance of macrophages is due to the accumulation of lipid droplets (LD) inside these cells. There is an upregulation of perilipin and the adipose differentiation-related protein in the endoplasmic reticulum–Golgi complex with the formation of vesicles containing lipids, phospholipids, cholesterol ester, and cholesterol. Further, increase in both the synthesis of LDL receptors induces a Th2 and Treg immune profile, with the production of IL-4 and IL-10, antibody production, absence of granulomas, and failure to restrict *M. leprae* growth.



Conclusion

Here we report two patients with RRMS diagnosed with lepromatous leprosy while on fingolimod. Both patients had a low ALC around the time of diagnosis and were identified to have a history of potential exposure.

Based on the mechanism of action of fingolimod and the immunopathology of leprosy, we suggest that fingolimod therapy may have played a significant role in the development of the infection.

References

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