A Review of Neurologic Complications of Biologic Therapy in Plaque Psoriasis

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PRACTICE **POINTS**

- Patients with a personal or strong family history of demyelinating disease should be considered for alternative treatment options before initiating anti–tumor necrosis factor (TNF) α therapy.
- Patients on biologic agents, especially TNF-α inhibitors, with subacute or rapidly progressive visual, motor, or sensory changes or a single neurologic deficit may warrant referral to neurology and/or neuroimaging.

The use of biologic medications has represented a great advancement in the treatment of moderate to severe plaque psoriasis and has improved patients' quality of life. Despite the increasing popularity of biologics, their neurological side effects have been a constant concern. Reports of demyelinating diseases associated with tumor necrosis factor α (TNF-α) inhibitors continue to accumulate. Additionally, efalizumab was withdrawn from the market in 2009 for causing progressive multifocal leukoencephalopathy (PML). These reports highlight the need for dermatologists to inform patients of the risks and promote informed decision-making with patients prior to starting a biologic agent. Dermatologists also need to recognize early manifestations of neurologic side effects. This review provides an overview of the literature on neurologic diseases that have been found to be associated with biologic agents used for plaque psoriasis. Clinical presentations and diagnostic workups of such diseases are given to aid dermatologists in their early diagnosis and referral.

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Biologic agents have provided patients with moderate to severe psoriasis with treatment alternatives that have improved systemic safety profiles and disease control[1]; however, case reports of associated neurologic complications have been emerging. Tumor necrosis factor α (TNF-α) inhibitors have been associated with central and peripheral demyelinating disorders. Notably, efalizumab was withdrawn from the market for its association with fatal cases of progressive multifocal leukoencephalopathy (PML).[2,3] It is imperative for dermatologists to be familiar with the clinical presentation, evaluation, and diagnostic criteria of neurologic complications of biologic agents used in the treatment of psoriasis.

Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a fatal demyelinating neurodegenerative disease caused by reactivation of the ubiquitous John Cunningham virus. Primary asymptomatic infection is thought to occur during childhood, then the virus remains latent. Reactivation usually occurs during severe immunosuppression and is classically described in human immunodeficiency virus infection, lymphoproliferative disorders, and other forms of cancer.[4] A summary of PML and its association with biologics is found in Table 1.[5-13] Few case reports of TNF-α inhibitor–associated PML exist, mostly in the presence of confounding factors such as immunosuppression or underlying autoimmune disease.[10-13] Presenting symptoms of PML often are subacute, rapidly progressive, and can be focal or multifocal and include motor, cognitive, and visual deficits. Of note, there are 2 reported cases of ustekinumab associated with reversible posterior leukoencephalopathy syndrome, which is a hypertensive

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TABLE 1. Clinical Presentation and Diagnostic Workup of PML Associated With Biologics

Biologic Agent[a]	Incidence of Associated PML	Clinical Presentation	Diagnostic Workup
Efalizumab[b]	3 cases in the absence of confounding factors (ie, HIV/AIDS, concurrent immunosuppressive therapy)[5]	Multifocal process resulting in diverse clinical manifestations: visual field defects, cortical blindness (20%–50% of patients and often the presenting manifestation[6]), motor weakness, gait abnormalities, incoordination, behavioral and cognitive abnormalities, single neurological deficit	MRI[7]; CSF studies: PCR for John Cunningham virus DNA; gold standard: brain biopsy[8]
Rituximab	1 in 25,000 RA patients[9]		
TNF inhibitors (infliximab, adalimumab, etanercept)[10-13]	Unknown		

Abbreviations: PML, progressive multifocal leukoencephalopathy; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RA, rheumatoid arthritis; TNF, tumor necrosis factor.
[a]Most reported cases of PML associated with biologic agents were in patients treated for nonpsoriatic diseases and have been confounded by the use of other immunosuppressive therapies or were unconfirmed PML.
[b]Approved for moderate to severe plaque psoriasis in 2003 but withdrawn from the market in 2009.

TABLE 2. Clinical Presentation and Diagnostic Workup of Demyelinating Disorders Associated With Biologics

Disorder	Biologic Agent	Incidence of Associated Demyelinating Disorder	Clinical Presentation	Diagnostic Workup
Optic neuritis: inflammatory demyelinating process of the optic nerve	Etanercept	49% of reported cases secondary to anti–TNF-α therapy (N=123)[17]	Onset over several hours and peaking 1–2 wk after initial presentation; periocular pain; unilateral loss of visual acuity; Uhthoff symptom: exercise/heat-induced deterioration of visual symptoms; Pulfrich phenomenon: misperception of direction of movement of an object; ipsilateral afferent pupillary defect; scotoma; optic disc pallor; loss of color vision	Clinical triad: visual loss, periocular pain, dyschromatopsia[18]; MRI; CSF analysis
	Infliximab	43% reported cases secondary to anti–TNF-α therapy (N=123)[17]		
	Adalimumab	7% reported cases secondary to anti–TNF-α therapy (N=123)[17]		
Multiple sclerosis: autoimmune inflammatory demyelinating disorder of the central nervous system	Etanercept	51% of reported cases secondary to anti–TNF-α therapy (N=55)[17]	Polysymptomatic onset occurring at 15–50 y of age; presenting symptoms include sensory disturbance (paresthesia and alterations in touch; pin-prick, vibration, facial, position, and postural sensations), weakness in the legs (more common) and arms, and visual disturbance[19]; ataxia; bladder problems; fatigue; Lhermitte sign; Uhthoff symptom (exacerbated by heat); optic neuritis and internuclear ophthalmoplegia	Definitive diagnosis: ≥2 symptomatic attacks (lasting >24 h, separated by at least 1 mo), with at least 1 attack confirmed by objective findings on either neurologic examination, visual evoked potential/response, or MRI; CSF studies
	Adalimumab	27% of reported cases secondary to anti–TNF-α therapy (N=55)[17]		
	Infliximab	20% reported cases secondary to anti–TNF-α therapy (N=55)[17]		

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Table 2. (continued)

Disorder	Biologic Agent	Incidence of Associated Demyelinating Disorder	Clinical Presentation	Diagnostic Workup
Transverse myelitis: immune-mediated spinal cord disorder with neurologic signs of motor, sensory, and autonomic spinal cord dysfunction	Etanercept[20]	Unknown	Associated with systemic autoimmune diseases (ie, RA, scleroderma, SLE); sensory: well-defined (cervical or thoracic) sensory level, below which pain and temperature sensation is altered; motor: initial limb flaccidity followed by hyperreflexia and Babinksi sign; autonomic: bowel and bladder incontinence, urinary urgency or retention, constipation, sexual dysfunction[22]	Clinical presentation, spinal MRI, CSF studies
Guillain-Barré syndrome: acute immune-mediated polyneuropathy characterized by rapidly progressive limb weakness and diminished or absent reflexes	Efalizumab[23]	Unknown	Two-thirds of cases have preceding respiratory or gastrointestinal tract symptoms ~3 wk before presentation[24]; symmetric, rapidly progressive, ascending bilateral weakness of the arms and legs with hyporeflexia or areflexia; limb numbness and pain; facial, respiratory, and bulbar muscle weakness; urinary retention and ileus	Clinical presentation, CSF studies, neurophysiology studies
	Adalimumab,[25,26] infliximab,[27] etanercept[27]	23 cases (adalimumab, n=7; infliximab, n=11; etanercept, n=5) of cases reported in literature to be associated with anti–TNF-α therapy[28]		

Abbreviations: TNF, tumor necrosis factor; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

encephalopathy characterized by headache, altered mental status, vision abnormalities, and seizures.[14,15] Fortunately, this disease is reversible with blood pressure control and removal of the immunosuppressive agent.[16]

Demyelinating Disorders

Clinical presentation of demyelinating events associated with biologic agents are varied but include optic neuritis, multiple sclerosis, transverse myelitis, and Guillain-Barré syndrome, among others.[17-28] These demyelinating disorders with their salient features and associated biologics are summarized in Table 2.[17-20,22-28] Patients on biologic agents, especially TNF-α inhibitors, with new-onset visual, motor, or sensory changes warrant closer inspection. Currently, there are no data on any neurologic side effects occurring with the new biologic secukinumab.[29]

Conclusion

Biologic agents are effective in treating moderate to severe plaque psoriasis, but awareness of associated neurological adverse effects, though rare, is important to consider. Physicians need to be able to counsel patients concerning these risks and promote informed decision-making prior to initiating biologics. Patients with a personal or strong family history of demyelinating disease should be considered for alternative treatment options before initiating anti–TNF-α therapy. Since the withdrawal of efalizumab, no new cases of PML have been reported in patients who were previously on a long-term course. Dermatologists should be vigilant in detecting signs of neurological complications so that an expedited evaluation and neurology referral may prevent progression of disease.

REFERENCES

1. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58:826-850.
2. FDA Statement on the Voluntary Withdrawal of Raptiva From the U.S. Market. US Food and Drug Administration website. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143347.htm. Published April 8, 2009. Accessed December 21, 2017.
3. Kothary N, Diak IL, Brinker A, et al. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *J Am Acad Dermatol*. 2011;65:546-551.
4. Tavazzi E, Ferrante P, Khalili K. Progressive multifocal leukoencephalopathy: an unexpected complication of modern therapeutic monoclonal antibody therapies. *Clin Microbiol Infect*. 2011;17:1776-1780.
5. Korman BD, Tyler KL, Korman NJ. Progressive multifocal leukoencephalopathy, efalizumab, and immunosuppression: a cautionary tale for dermatologists. *Arch Dermatol*. 2009;145:937-942.
6. Sudhakar P, Bachman DM, Mark AS, et al. Progressive multifocal leukoencephalopathy: recent advances and a neuro-ophthalmological review. *J Neuroophthalmol*. 2015;35:296-305.
7. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80:1430-1438.

8. Koralnik IJ, Boden D, Mai VX, et al. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52:253-260.
9. Clifford DB, Ances B, Costello C, et al. Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. *Arch Neurol*. 2011;68:1156-1164.
10. Babi MA, Pendlebury W, Braff S, et al. JC virus PCR detection is not infallible: a fulminant case of progressive multifocal leukoencephalopathy with false-negative cerebrospinal fluid studies despite progressive clinical course and radiological findings [published online March 12, 2015]. *Case Rep Neurol Med*. 2015;2015:643216.
11. Ray M, Curtis JR, Baddley JW. A case report of progressive multifocal leucoencephalopathy (PML) associated with adalimumab. *Ann Rheum Dis*. 2014;73:1429-1430.
12. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. *Arthritis Rheum*. 2010;62:3191-3195.
13. Graff-Radford J, Robinson MT, Warsame RM, et al. Progressive multifocal leukoencephalopathy in a patient treated with etanercept. *Neurologist*. 2012;18:85-87.
14. Dickson L, Menter A. Reversible posterior leukoencephalopathy syndrome (RPLS) in a psoriasis patient treated with ustekinumab. *J Drugs Dermatol.* 2017;16:177-179.
15. Gratton D, Szapary P, Goyal K, et al. Reversible posterior leukoencephalopathy syndrome in a patient treated with ustekinumab: case report and review of the literature. *Arch Dermatol*. 2011; 147:1197-1202.
16. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334:494-500.
17. Ramos-Casals M, Roberto-Perez A, Diaz-Lagares C, et al. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev*. 2010;9:188-193.
18. Hoorbakht H, Bagherkashi F. Optic neuritis, its differential diagnosis and management. *Open Ophthalmol J*. 2012;6:65-72.
19. Richards RG, Sampson FC, Beard SM, et al. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. *Health Technol Assess*. 2002;6:1-73.
20. Caracseghi F, Izquierdo-Blasco J, Sanchez-Montanez A, et al. Etanercept-induced myelopathy in a pediatric case of blau syndrome [published online January 15, 2012]. *Case Rep Rheumatol*. 2011;2011:134106.
21. Fromont A, De Seze J, Fleury MC, et al. Inflammatory demyelinating events following treatment with anti-tumor necrosis factor. *Cytokine*. 2009;45:55-57.
22. Sellner J, Lüthi N, Schüpbach WM, et al. Diagnostic workup of patients with acute transverse myelitis: spectrum of clinical presentation, neuroimaging and laboratory findings. *Spinal Cord*. 2009;47:312-317.
23. Turatti M, Tamburin S, Idone D, et al. Guillain-Barré syndrome after short-course efalizumab treatment. *J Neurol*. 2010;257:1404-1405.
24. Koga M, Yuki N, Hirata K. Antecedent symptoms in Guillain-Barré syndrome: an important indicator for clinical and serological subgroups. *Acta Neurol Scand*. 2001;103:278-287.
25. Cesarini M, Angelucci E, Foglietta T, et al. Guillain-Barré syndrome after treatment with human anti-tumor necrosis factor alpha (adalimumab) in a Crohn's disease patient: case report and literature review [published online July 28, 2011]. *J Crohns Colitis*. 2011;5:619-622.
26. Soto-Cabrera E, Hernández-Martínez A, Yañez H, et al. Guillain-Barré syndrome. Its association with alpha tumor necrosis factor [in Spanish]. *Rev Med Inst Mex Seguro Soc*. 2012;50:565-567.
27. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barré and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. *Arthritis Rheum*. 2006;54:1429-1434.
28. Alvarez-Lario B, Prieto-Tejedo R, Colazo-Burlato M, et al. Severe Guillain-Barré syndrome in a patient receiving anti-TNF therapy. consequence or coincidence. a case-based review. *Clin Rheumatol*. 2013;32:1407-1412.
29. Garnock-Jones KP. Secukinumab: a review in moderate to severe plaque psoriasis. *Am J Clin Dermatol*. 2015;16:323-330.