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Considerations on the appropriateness of the John Cunningham virus antibody assay use in patients with rheumatoid arthritis☆

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ABSTRACT

Objective: The John Cunningham virus (JCV) is a generally benign and asymptomatic polyomavirus. Due to an association of the anti-integrin agent natalizumab with progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis (MS), a newly developed anti-JCV antibody assay has been implemented as a risk-stratification tool for natalizumab-treated patients with MS. This viewpoint offers insight and perspective regarding the potential unapproved use of the anti-JCV antibody assay in rheumatoid arthritis (RA) and examines how rheumatologists can best assist patients.
Methods: A primary literature search was conducted to identify articles on the number of cases of PML associated with natalizumab in patients with MS, the number of cases of PML associated with patients with rheumatic disease, PML incidence in the general population, serum-based assays to detect JCV exposure, and clinical PML presentation and treatment methods.
Results: Risk of PML in patients with RA receiving biologics appears orders of magnitude lower than that expected in natalizumab-treated patients with MS (1 in 1000). If patients with RA are risk stratified assuming an anti-JCV antibody seropositivity of 60%, theoretically 23,400 anti-JCV antibody-positive patients would have to receive rituximab before potentially observing 1 PML case.
Conclusions: Data currently indicate that rheumatologists should not order the anti-JCV antibody assay for patients requiring biologics. Monitoring relevant symptoms indicative of emerging PML might provide greater value to patients, thus prompting interventional measures that could affect prognosis.
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Introduction

The John Cunningham virus (JCV) is a generally benign and asymptomatic polyomavirus. Similar to other viruses, such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV), its prevalence is high in the general population [1,2]. Most exposures occur in childhood; however, rates of infection increase with age: 10% of children aged 1–5 years are positive for the JCV antibody compared with 40–60% aged 10 years, 50% aged 20–29 years, and 68% aged 60–100 years [3–5]. Consequences of either EBV or CMV infections are generally benign but can lead to severe complications. For example, EBV infection can lead to lymphoma development after immunosuppressant exposure and CMV infection to CMV-related retinitis in patients with human immunodeficiency virus (HIV) [6,7]. Similarly, JCV causes no clinical illness at the time of infection but can, in rare circumstances, lead to progressive multifocal leukoencephalopathy (PML)—a demyelinating disease of the central nervous system (CNS) that is often lethal or can result in permanent neurological sequelae [8]. This viewpoint offers insight and perspective regarding the potential unapproved use of the anti-JCV antibody assay in rheumatoid arthritis (RA) and examines how rheumatologists can best assist patients.

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis.

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Literature search methodology

A primary literature search was conducted to identify articles on the number of cases of PML associated with natalizumab in patients with MS, the number of cases of PML associated with patients with rheumatic disease, PML incidence in the general population, serum-based assays to detect JCV exposure, and clinical PML presentation and treatment methods.

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PML and immunomodulation

Several critical steps must occur to induce PML, explaining the disconnect between the high JCV infection rate in the general population and the extremely low-observed PML incidence. For a productive infection to occur, JCV must undergo gene rearrangement(s), be re-expressed from latent or persistent sites, and lastly, because of failed CNS immunosurveillance, enter the brain and infect glial tissues [8]. Importantly, PML development depends on alterations in a patient's immune response, as exemplified by reports of PML in patients with suppressed immune systems due to HIV infection or cancer. Interestingly, whereas PML was initially reported in ~5% of patients with HIV, introduction of effective antiretroviral therapies led to subsequent improvement of a patient's immune system and significant reductions in PML cases [9,10].

Despite the frequency of immunosuppressive treatment for multiple sclerosis (MS) or inflammatory bowel disorders, PML was not reported until 2005, when 3 cases (2 with MS and 1 with Crohn disease) associated with natalizumab, a new anti-integrin agent, were presented; these events led to its market withdrawal [8]. Because of the otherwise beneficial effects in MS, natalizumab was reintroduced after risk-mitigation strategies and a controlled distribution program were devised.

As of September 2, 2014, 495 PML cases were reported in patients with MS exposed to natalizumab [11]. With the caveat that reporting in controlled programs is likely greater than with voluntary submission, this number contrasts with the few cases reported for other immunosuppressant drugs/autoimmune diseases. A total of 34 confirmed cases were identified in patients with rheumatic diseases exposed to synthetic and biologic disease-modifying antirheumatic drugs [12].

Although very rare in RA, PML can be devastating, thus justifying efforts to mitigate individual patient risk. Given the successful implementation of a risk-mitigation strategy in natalizumab-treated patients with MS using a newly developed anti-JCV antibody assay, we wondered whether a similar approach could be applied to other diseases for which PML has been reported in association with immunosuppressant[13,14]. Specifically, could the anti-JCV antibody assay assist in estimating PML risk in conditions such as RA?

Serum-based assay to detect JCV exposure

The JCV Stratify assay, developed to detect JCV-specific antibodies in the serum of patients with MS, is an enzyme-linked immunosorbent assay (ELISA). Of patients with MS treated with natalizumab, 54% were positive for anti-JCV antibodies, with a false-negative rate of 2.5% [15]. Retrospective analyses of large patient cohorts indicated that patients with MS—who were JCV seropositive, had prior immunosuppressant exposure, and were treated with natalizumab for ≥24 months—were at significantly greater risk of developing PML (Table 1) [13,15,16]. Whereas this algorithm does not indicate or mandate that individuals with an estimated higher risk should not receive natalizumab, it helps physicians estimate the benefit/risk and discuss treatment options with patients. Although a negative test could be interpreted as no PML risk, it is worth noting that, as stated above, the anti-JCV test can give false-negative results [15,17]. Patients with negative JCV antibody test results excreted the virus in urine in 37% of cases or were shown to have positive T-cell responses to the virus, indicating prior exposure [17,18]. Consideration should also be given to the potential need to repeat negative tests, given the ~2% annual seroconversion rate [15].

Table 1
Estimated incidence of PML in the United States stratified by risk factor [16]

Anti-JCV Ab negative	Natalizumab exposure (months)	Anti-JCV Ab positive	
		No prior immunosuppressant use	Prior immunosuppressant use
1/1000	1–24	<1/1000	1/1000
	24–48	3/1000	13/1000
	49–72	7/1000	9/1000

Ab, antibody; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy.

Physicians contemplating using the JCV antibody assay in patients with RA should note that the assay has not been validated or proven to have clinical utility in this population, in striking contrast with its demonstrated clinical utility as a risk-stratifying tool in patients with MS exposed to natalizumab [19]. In anti-JCV antibody-positive patients with MS and no prior immunosuppressant use, serum/plasma antibody levels, measured as index, may differentiate PML risk [19]. No data on JCV antibody assay use in RA have been reported. Whereas in patients with MS, overall JCV seropositivity is estimated at 50–60% and higher (66.5%) in patients aged ≥60 years (consistent with the general population), seropositivity is possibly greater in patients with RA, who tend to be older [5,14,20]. Assay validation in non-MS patient cohorts is lacking. ELISA-based, the JCV antibody assay is susceptible to interferences, in particular from rheumatoid factor, present in up to 70% of patients with RA and a major source of interference in immunoassays [21]. In fact, the JCV antibody assay package insert specifies that samples containing antinuclear antibodies or rheumatoid factor have not been evaluated and may cause erroneous results [22].

Considerations on PML risk-mitigation across diseases

PML incidence rate in patients with RA is ~3-fold higher than in the general population (1.0 vs 0.3/100,000 person-years) [23]. PML is frequently associated with biologic use although it has, very rarely, been reported in biologic-naive patients [23]. The US Food and Drug Administration (FDA) Adverse Event Reporting System database had 10 confirmed PML cases in patients with RA reported through March 31, 2010: 6 received rituximab, 1 infliximab, and 3 nonbiologic immunosuppressive agents [12]. Risk of PML in patients with RA receiving biologics appears orders of magnitude lower than that expected in natalizumab-treated patients with MS (1 in 1000, incidence increases with increasing exposure time; Table 1) [16,23]. A recently proposed classification of therapies associated with PML assigned natalizumab and rituximab to distinct classes [8]. Class 1 agents including natalizumab unequivocally introduce substantially increased PML risk regardless of preexisting conditions, whereas class 2 agents such as rituximab appear to increase PML risk at significantly lower levels than class 1 agents, and most patients have either underlying conditions or receive other medications recognized to increase PML risk.

Risk mitigation in natalizumab-treated patients with MS identifies higher-risk patients on the basis of JCV antibody assay positivity, duration of treatment, and prior use of other immunosuppressants [13]. Efforts have yet to identify clear unifying factors in rheumatic diseases [12,24,25]. In systemic lupus erythematosus (SLE), PML risk is 10-fold greater than in RA, indicating that the underlying condition is itself a risk [25]. Cases of rituximab-associated PML have often been characterized by potentially confounding factors such as underlying diagnoses (SLE,

Table 2
Reporting rate of confirmed PML in patients with RA treated with rituximab[a]

	Anti-JCV Ab positive	Anti-JCV Ab negative	Overall
PML, *n*	8	0	8
No PML, *n*	187,189	124,798	311,987
Total, *n*	187,197	124,798	311,995
Reporting rate per 100,000 unique patients (95% CI)	4.3 (1.9–8.4)	0 (0–3.0)	2.6 (1.1–5.1)
Patients requiring treatment to identify 1 PML case, *n*	23,400	–	–

Ab, antibody; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis.

[a] Numbers were calculated using Genentech data and based on the assumption that, in rituximab-treated patients with RA, the prevalence of anti-JCV seropositivity is 60%. However, in RA, the prevalence of anti-JCV seropositivity in rituximab-treated patients has neither been tested nor confirmed. The estimated worldwide cumulative exposure to rituximab from marketing experience has been taken from the 2015 periodic benefit–risk evaluation report (1062808).

lymphoproliferative disorders, and Sjögren syndrome) and prior immunosuppressant use [8,26]. Although prior exposure to JCV is likely the least common denominator in the emergence of PML in either natalizumab-treated patients with MS or biologic-treated patients with rheumatic diseases, the algorithm developed for natalizumab-treated patients with MS should not be readily extrapolated to other diseases. The (fortunate) lack of enough cases in rheumatic diseases impedes analyses required to identify potential predisposing conditions specific to RA. Commenting on an anti-integrin similar to natalizumab, the FDA recently cautioned against extrapolating findings across different treatments, populations, and environments [27].

Because of the low PML incidence reported in patients with RA, the potential positive predictive value of the anti-JCV assay would be too low to serve as a valuable risk-mitigation option. If patients with RA are risk stratified assuming an anti-JCV antibody seropositivity of 60%, theoretically 23,400 anti-JCV antibody-positive patients would have to receive rituximab before potentially observing 1 PML case (Table 2). The test would not be informative in predicting risk, and positive results could produce unnecessary anxiety, warranting additional patient counseling.

Practical PML clinical considerations

Although a PML-predicting test is desirable, the current assay provides only a means to demonstrate virus exposure. Data currently indicate that rheumatologists should not order the anti-JCV antibody assay for patients requiring biologics. Monitoring relevant symptoms indicative of emerging PML might provide greater value to patients, thus prompting interventional measures that could affect prognosis. PML manifests clinically through neurological symptoms, such as impaired vision, motor weakness, and changes in mentation [28]. Although neurological examinations are uncommon when assessing patients with RA, some simple assessments are not an insurmountable task for rheumatologists. Neurology experts have devised a simple questionnaire assessing recent changes in vision, speech, gait, sensation, comprehension, coordination, and personality to monitor patients in clinical trials evaluating therapeutics with PML risk (Table 3) [29]. Routine monitoring is important because early diagnosis and treatment withdrawal are the most significant prognostic factors affecting outcome [30].

Table 3
Clinical trials subjective checklist of relevant neurological signs and symptoms for PML safety assessment[29]

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "yes," obtain a description of the symptom(s) with examples	Applicable objective test(s): document results on PML objective checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility.
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barre maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Ability to follow serial commands.
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

PML, progressive multifocal leukoencephalopathy.

Conclusion

Impaired cognitive functions in patients with RA receiving biologics may be more than a manifestation of aging. Lacking predictive tests, physicians should be alert for the very rare case of PML and be prepared to rapidly query a few neurological signs and symptoms, enabling prompt implementation of measures that can drastically improve prognosis and outcome, such as immediate suppression of the offending agent [8,30].

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