ABSTRACT

Introduction

Progressive Multifocal Leukoencephaly (PML) is an opportunistic central nervous system infection with John Cunningham Virus (JCV) that is potentially fatal or severely debilitating. Most neurologists think the risk of PML with JCV positive patients, treated with either fingolimod or dimethyl fumarate is so low that they avoid testing or discussing it with patients.

Patients and Methods

Patients that were offered testing for JCV readily accepted the option, despite being advised that most neurologists would not order the test and would take little note of the result.

Results

The 4 patients who were positive for testing for JCV all opted to change treatment to a perceived less efficacious medication, which has no reported cases of PML associated with it.

Discussion

The Australian case of *Rogers vs Whitaker* set the benchmark for material risk consideration in which such risk should be respected when doctors discuss treatment with patients. In *Rogers* the risk was 1/14,000 while for fingolimod the risk is 1/10,000, if JCV positive, and less so for dimethyl fumarate. This report confirms that even these low risks directly influence patient choices and leave clinicians liable in negligence if not informing patients who subsequently develop PML.

INTRODUCTION

Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic central nervous system (CNS) infection with the John Cunningham polymavirus (JCV), which targets oligodenrocytes and astrocytes, causing cell death [1]. It is potentially fatal and, if not, may cause severe disability [2].

PML occurs in the face of immunosuppression and has been reported in patients with multiple sclerosis (MS), especially those treated with such agents as natalizumab [3]. More recently it has also been reported in MS patients treated with fingolimod [4] and dimethyl fumarate [5]. The presence of JCV does not necessarily result in PML with the risk of PML with fingolimod, who are JCV positive, being ~ 1/10,000 and that with dimethyl fumarate being far less well established but thought to be considerable less than with fingolimod [6 – 7].

In talking with colleagues it appears that key opinion leaders, in the field of MS management, feel that the risk of PML, even in those who are JCV positive, is so low that it does not justify further discussion with patients. The consensus, from talking with colleagues, is that even testing for JCV status is unjustified and discussing JCV and PML introduces an unnecessary fear for patients with MS, which is already an emotionally charged diagnosis for patients [8].

This concept raises legal medicine questions of right to know, material risks and brings into focus the changing landscape of patient rights and attitudes.

PATIENTS AND METHODS

Acknowledging my perception of the attitudes of colleagues, while concurrently recognising the growing reports of PML in patients with MS, including those on fingolimod and dimethyl fumarate [5 – 9], patients were offered the option of being tested for JCV. They were advised that most neurologists felt the inherent risks were so low that they would not so test and also would not change treatment, should the JCV status prove positive.

Patients were informed that the prevailing prevalence of PML in JCV positive patients was ~1/10,000 for Gilenya (fingolimod) and thought to be considerably lower for Tecfidera (dimethyl fumarate). They were given the option to have the test and to discuss the results once the test results were available.

RESULTS

All patients offered the option of being tested for JCV status accepted the offer without reservation. At the time of writing, 4 patients who were JCV positive, opted to change medication from their current regimen. These included:

LJ, a 62 year old female who had been treated with fingolimod since 2011 for relapsing remitting MS with marked lymphopenia, down to 0.44 E9/L, and JCV positive (Index Value 3.23) but otherwise symptom-free re MS. She opted to change from fingolimod to teriflunomide (Aubagio) in September 2017 and has remained symptom-free with normalisation of her full blood count and without adverse events or MS relapses.

CA, a 61 year old female, who was treated with fingolimod since 2010, for relapsing remitting MS, had lymphopenia, down to 0.46 E9/L, and was JCV positive (Index Value 3.65), although symptom-free re MS. She commenced teriflunomide in September 2017 with normalisation of full blood count, no adverse events and no MS relapses.

MW, a 39 year old man with relapsing remitting MS, diagnosed in 2016, was treated with fingolimod and JCV was negative at the time. Repeat screening for JCV, tested when lymphocyte count was down to 0.34 E9/L was positive (Index Value 3.88) and he opted to change treatment to teriflunomide. When last seen, 2 months later, he was symptom free, feeling well with normalised full blood count.

SG, a 56 year old female, recently diagnosed with relapsing remitting MS, in 2017, commenced dimethyl fumarate with mild lymphopenia (down to 0.71 E9/L), whose JCV status was positive (Index Value 3.48). She opted to stop the dimethyl fumarate and commenced teriflunomide early in 2018 but it is too early to report her response to change in treatment.

DISCUSSION

PML is a serious complication following immunosuppression in MS [1-9], although the reported risk thereof with fingolimod is 1/10,000 [6] and thought to be much less than that with dimethyl fumarate, [7] even in the presence of JCV positive status. This has resulted in colleagues being unwilling to test for JCV status or to discuss it with patients.

The seminal legal medicine case, in Australia, was that of *Rogers v Whitaker* [10], which was a quarter of a century ago. In that case, the patient, Maree Whitaker, had 40 years of total right eye blindness following an injury at age 9 years, but lived a full life. Christopher Rogers, an ophthalmologist, offered restorative surgery to the eye, which he conducted with appropriate skill and care. Following same, Whitaker developed "sympathetic ophthalmia" in her left eye, without improvement in her right eye, causing bilateral, almost total blindness. She successfully sued in negligence for failure to warn, even though she had not asked about effects on the left eye. The risk of "sympathetic ophthalmia" was quoted to be 1/14,000 and it need not necessarily cause blindness in the affected eye (as was the case with Whitaker).

The Court decided that a medical practitioner "…has a duty to warn a patient of a material risk inherent in the proposed treatment…" and defined a material risk as one which "…a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it or if the medical practitioner is or should reasonably be aware that the particular patient, if warned of the risk, would be likely to attach significance to it (page 490).

These comments, from *Rogers v Whitaker,* are highly relevant to the cases being presented in this report. Of the 4 JCV positive cases, all of whom were advised that, more probably than not, most colleagues would have neither tested for JCV status nor suggested consideration of changing treatment, due to positive JCV measurement (because of the very low risk of PML), all 4 patients chose to have the test and, further, to change treatment because of the results.

The risk of PML with fingolimod is considerably higher than was the risk of 'sympathetic ophthalmia' in *Rogers v Whitaker* in which the ophthalmologist was held negligent for failure to warn. The fact that all patients, offered the opportunity to change treatment, based on the very low likelihood of risk, confirms that the risk is material for the reasonable patient. It follows that the first patient to develop PML with MS, being treated with either fingolimod or dimethyl fumarate, will be able to cite *Rogers,* a High Court of Australia decision, where the risk was far less than 1/10,000 as is the case with fingolimod [(6)]. The experience in which all patients, offered consideration for change, opted for change has confirmed the material nature of the risk.

One criticism of the change in treatment is the perceived relative reduced efficacy of teriflunomide, as compared with either fingolimod or dimethyl fumarate [(11,12)], although there have been no reported cases of PML associate with teriflunomide treatment. This may also be material in the patient's decision and, in the third case presented, the patient, having been advised potentially lower protective efficacy, responded by accepting same but also stressing that the change to lower perceived efficacy did not preclude re-escalation should relapse occur.

There is considerable evidence to suggest that relapses are less likely as the duration of disease of MS progresses [(13)]. Both cases 1 and 2 had been in remission while being treated with fingolimod for at least 7 years, thereby suggesting good disease control. It was advised that efficacy with teriflunomide was perceived as less potent than is the case with fingolimod but that there is suggestion that as the disease progressed the likelihood of relapse was also reduced [(13)]. This might also suggest that even if teriflunomide was less potent than fingolimod [(14)] the MS may not require the same intensity of treatment to maintain the status quo.

In conclusion, this paper raises the concern of successful litigation if not testing or discussing JCV status in patients treated with medications known to be associated with PML, if PML eventuates. The experience shared confirms the 'material risk' nature of the warning and discussion of which the doctor "should reasonably be aware". The patients reported, chose to act upon warning of such risk; even if extremely low.

REFERENCES:

1. Adang, L. and Berger, J. (2015) Progressive Multifocal Leukoencephalopathy. *F1000Research.*

2. Pavlovic, D., Patera, A., Nyberg, F., Gerber, M. and Liu, M. (2015).

   Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Therapeutic Advances in Neurological Disorders,* 8(6), pp.255-273.

3. Boster, A., Nicholas, J., Topalli, I., Kisanuki, Y., Pei, W., Morgan-Followell, B., Kirsch, C., Racke, M. and Pitt, D. (2013). Lessons Learned From Fatal Progressive Multifocal Leukoencephalopathy in a Patient With Multiple Sclerosis Treated With Natalizumab. *JAMA Neurology,* 70(3), p.398.

4. Berger, J. (2017). Classifying PML risk with disease modifying therapies. *Multiple Sclerosis and Related Disorders*, 12, pp.59-63.

5. Rosenkranz T, Novas M, TerborgC .(2015). PML in a patient with lymphocytopenia treated with dimethyl fumarate. *New England Journal of Medicine,* 372, pp.1476–1478.

6. Novartis Pharmaceuticals Q4 2017 Financial Report dated Januay 2018-03-19

7. Joanna, B. (2017). JC Virus and MS: What You Need to Know. [online] EverydayHealth.com. Available at: https://www.everydayhealth.com/multiple-sclerosis/treatment/jc-virus-ms-what-you-need-know/ [Accessed 21 Mar. 2018].

8. Sá, M. (2008). Psychological aspects of multiple sclerosis. *Clinical Neurology and Neurosurgery*, 110(9), pp.868-877.

9. Rukovets, O., 2013. FDA Investigates PML in Patient Taking Gilenya. *Neurology Today.*13(24), pp.23-24.

10. Rogers v Whitaker (1992) 175 CLR 479.

11. Guarnera, C., Bramanti, P. and Mazzon, E. (2017). Comparison of efficacy and safety of oral agents for the treatment of relapsing and remitting multiple sclerosis. *Drug Design, Development and Therapy*,11, pp.2193-2207.

(References continued):

12. Nicholas, J., Boster A., Wu, N., YiHuang, M., Riester, K., Jhaveri, M., Edwards, M., Lee A. (2017). Comparative effectiveness of delayed-release dimethyl fumarate versus fingolimod and teriflunomide on risk of relapse. *Neurology*, 88 (16 Supplement) P6.375;

13. Tremlett, H., Yousefi, M., Devonshire, V., Rieckmann, P. and Zhao, Y. (2009). Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology*, 73(20), pp.1616-1623.

14. Kalincik, T. (2017). Effectiveness of fingolimod, dimethyl fumarate and teriflunomide in relapsing-remitting multiple sclerosis: a comparative longitudinal study. *ECTRIMS Online Library*.

15. Birnbaum, G. (2017). Stopping Disease-Modifying Therapy in Nonrelapsing Multiple Sclerosis. *International Journal of MS Care,* 19(1), pp.11-14.

John Cunningham Virus Status And Progressive Multifocal Leukoencephalopathy As Material Risks When Treating Relapsing Remitting Multiple Sclerosis

Authors: Roy G Beran [1,2,3]
Sandiya Sathiyseelan [3]
John Devereux [4]

Institutions:

1. University of New South Wales,
   South Western Clinical School of Medicine, Sydney, Australia
2. Griffith University,
   School of Medicine, Queensland, Australia
3. Strategic Health Evaluators,
   Level 6, 12 Thomas Street, Chatswood NSW 2067
4. University of Queensland, Australia

Title character count: 79

Number of references: 15
Number of tables: N/A
Number of figures: N/A

Word count abstract: 195
Word count paper: 1375

Corresponding Author:
Roy G Beran
Suite 6, 12 Thomas Street\
Chatswood, NSW 2067
Phone: 02-9415-3800
Fax: 02-9413-1353
roy.beran@unsw.edu.au

Sandiya Sathiyseelan research@sheresearch.com
John Devereux j.devereux@law.uq.edu.au

Search Terms: Multiple Sclerosis, All ethics in Neurology/ Legal issues, Malpractice, Professional conduct and ethics, Failure to warn

*These authors contributed equally to the manuscript.

Author Contributions:
Roy G Beran, initially developed the concept of the report, contributed to writing and evolution of the concept and its editing.

Sandiya Sathiyseelan, contributed to the writing and editing.

John Devereux, helped develop and expand the concept, reviewed the content and further appraised the legal precedence review. Also contributed to the writing and editing.

Author Disclosures:
Roy G Beran – Reports no disclosures
Sandiya Santhiyseen – Reports no disclosures
John Devereux – Reports no Disclosures