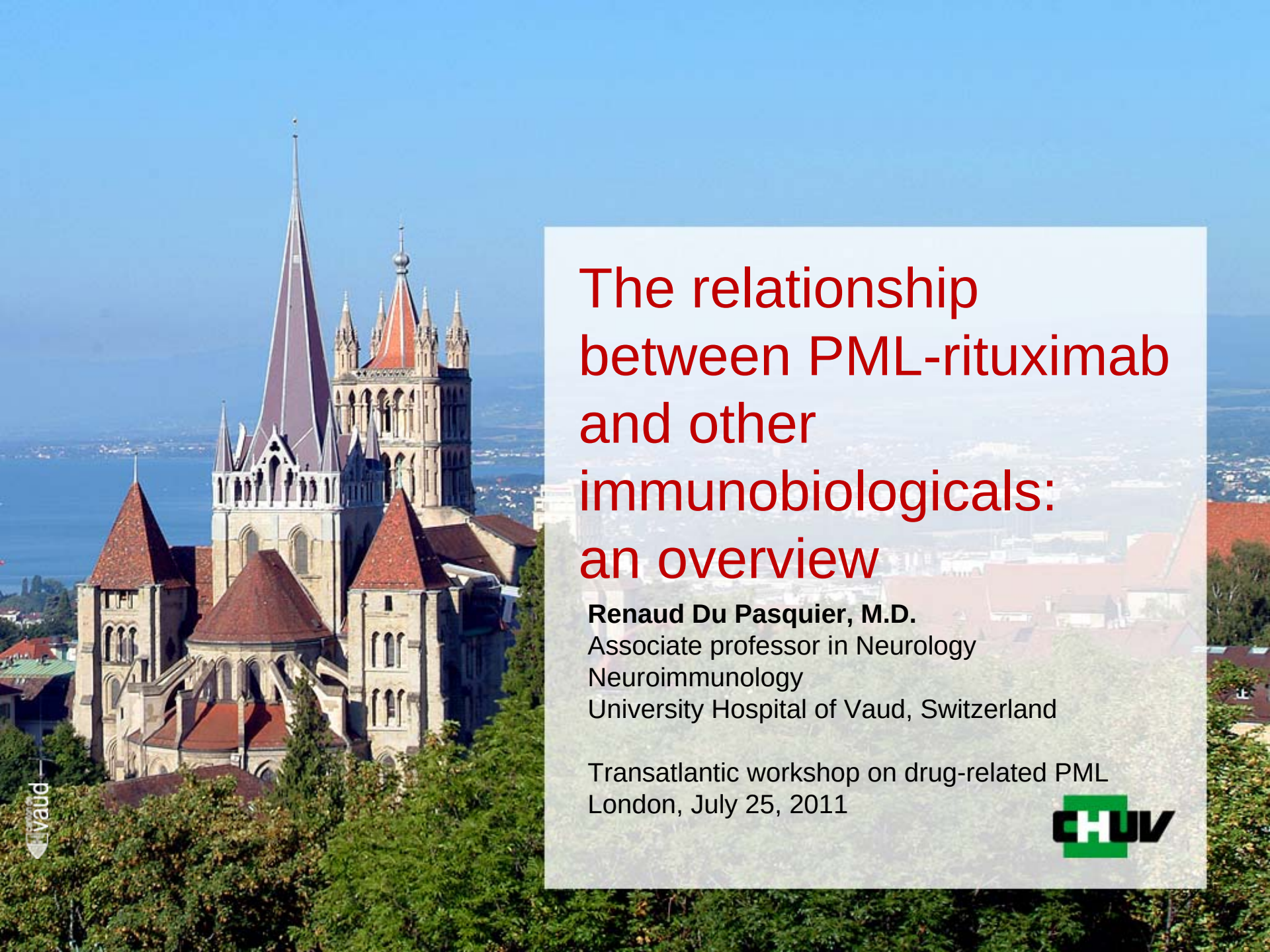


The relationship between PML-rituximab and other immunobiologicals: an overview

Renaud Du Pasquier, M.D.
Associate professor in Neurology
Neuroimmunology
University Hospital of Vaud, Switzerland

Transatlantic workshop on drug-related PML
London, July 25, 2011

PML hits from 2004 to July 2011 in the WHO database

- Warnings:
  - not all countries report and not all cases are reported → undereporting
  - Tendency to report mostly the PML cases associated with novel drugs → **notoriety bias**
  - A single case of PML will appear with each of the drug administred
    → overestimation of the number of PML

  => Not more than a rough estimation

Conventional agents	PML hits
Corticosteroids	116
Azathioprine	14
Carboplatin	8
Ciclosporin/ Tacrolimus	43
Cisplatin	17
Cyclophosphamide	79
Cytarabin	18
Doxorubicin	21
Etoposide	18
Fludarabine	68
Mitoxantrone	11
Mycophenolate mofetil	35
Vincristine	31

mAbs	PML hits
Alemtuzumab	28
Efalizumab	13
Infliximab	15
Natalizumab	157
Rituximab	238

>21 mAbs are marketed

Keene Can J Neurol Sci, 2011

Rituximab

- Anti CD-20 => pre-B and B cell depletion (but not of stem cell or plasma cells)
- Indication recognized in:
  - Non Hodgkin lymphoma (NHL)
  - Chronic lymphocytic leukemia (CLL)
  - Moderate to severe rheumatoid arthritis (RA) in 2d intention
  - Systemic lupus erythematosus (SLE): non-recognized indication but frequently administred
  - MS?

PML after rituximab in HIV-neg pts

- 57 HIV-neg pts: lymphoma/leukemia (52), autoimmune dis. (5) including 2 SLE
- Always given with other immunosuppressive drugs, mostly steroids
- Median interval between last dosis and diagnosis: 5.5 month
- 90% mortality, death in 2 months
- 30 cases of SLE without rituximab…

=> Is rituximab really confering an added risk of PML?

Carson, Blood 2009;113:4834-4840

Unusual viral infections in pts with autologous stem cell transplantation

- 338 pats had bone marrow transplant pre-conditioning
- 276: carmustine, etoposide, cytarabine and cyclophosphamide --> Ø viral infections
- 62: idem + rituximab --> 2 PML and 2 CMV systemic infections (p=0.03 for PML)

- => evidences that rituximab contributes to increase the risk of PML occurrence

Goldberg, Blood 2002;99:1486-88

Rituximab, NHL and PML

- Retrospective monocentric cohort study
- 976 NHL patients from 1994 to 2008
- 517 (53%): at least 1 dosis of rituximab

Parameter	Rituximab exposed (n = 517)	Rituximab unexposed (n = 459)	p-value
Mean age at diagnosis of non-Hodgkin's lymphoma ± standard deviation, yrs	58.3 ± 14.1	61.5 ± 14.0	<.001
Male, n (%)	285 (55.1)	206 (44.9)	.002
Brain imaging, n[a] (%)	38 (7.4%)	35 (7.6)	.903
Grade[b] (aggressive)	238 (46.0)	222 (48.4)	.480
Stage[c] (advanced)	76 (14.8)	82 (17.9)	.397
Progressive multifocal leukoencephalopathy	5	0	–
Person-years	2,083	2,147	–
Incidence rate x 1000 pts-year	2.4 (1.0-5.6)	0.0 (0.0-1.8)	

Tuccori, The Oncologist 2010

Rheumatoid arthritis (RA) and PML

- PML is a very rare complication of RA
  - No PML in >72'000 RA patients *Amend, Neurology 2010*
  - 0.4/1000'000 RA pts *Calabrese and Molloy Arthritis Rheum 2009*

Incidence of PML in HIV-neg pts

Table 4 Incidence rates of chart-confirmed progressive multifocal leukoencephalopathy during follow-up by cohort

Cohort	Cases[a]	Person-years[b]	Incidence rate[c]	95% Confidence interval
SLE	1	42,278	2.4	0.1-13.2
RA	0	133,852	0.0	0.0-2.2
Autoimmune vasculitis	1	9,226	10.8	0.3-60.4
MS	0	57,117	0.0	0.0-5.2
Sjögren disease	0	13,717	0.0	0.0-21.8
NHL	3	36,161	8.3	1.7-24.2
CLL	1	9,025	11.1	0.3-61.7
Solid organ transplant	0	11,172	0.0	0.0-26.8
Bone marrow transplant	1	2,824	35.4	0.9-197.3
General population	0	690,993	0.0	0.0-0.4
NHI	0	7,946,397	0.0	0.0-0.0

Amend, Neurology 2010;1326-32

Rituximab, RA and PML

- 5 cases of PML in 129’000 RA pts exposed to rituximab, including one patient with minimal immunosuppression

  => PML ~1/25’000 rituximab-exposed pts

Clifford, Arch Neurol 2011
Fleischmann, Arthritis Rheum 2009

PML and efalizumab

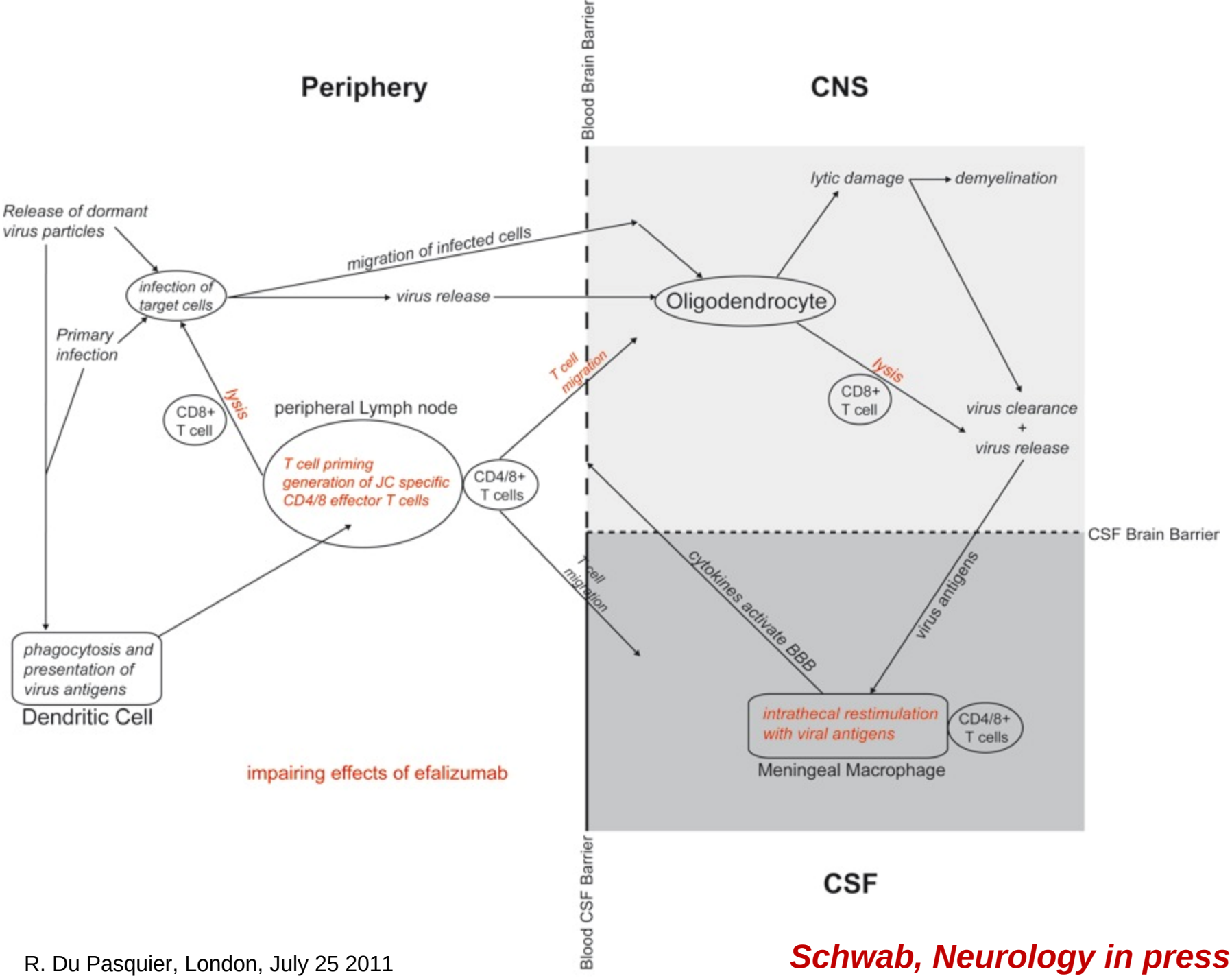
- Anti CD11a IgG1 Ab.
- Indication: psoriasis
- 166 pts > 3 years
- 3 proven + 1 suspected PML, all having received efalizumab >3 years, monother.

$\Rightarrow$Voluntarily withdrawn in spring 2009

- Estimated incidence of PML ~1/40 if tt>3 y

Berger, mAbs 2009

Keene, Can J Neurol Sci 2011



Schwab, Neurology in press

PML and alemtuzumab

- Anti-CD52 mAb=> ↓ 95% of B/T cells > 2 y
- NHL, CLL, ….MS?
- 3 cases of PML
  - 1 PML 3 months after start treatment for CLL
  - 1 T cell lymphoma with multiple immuno↓ drugs
  - 1 lung transplant recipient, also with other immuno↓ drugs

Berger, mAbs 2009

Keene, Can J Neurol Sci 2011

PML and anti-TNFα

- RA, psoriatric arthritis, ankylosing spondylarthritis
- Lenercept worsens RR-MS ***Neurology 1999***
- BIOGEAS: large Spanish prospective multi-center data bank on side effects of biological agents
- Complications: MS-like disease, optic neuritis, demyelinating peripheral neuropathies, but not PML

Lysandropoulos, Curr Opin Neurol 2010
Bosch, Nat Rev Neurol 2011

CONCLUSION

- Rituximab most probably confers an added risk of PML when administred to patients with PML-favoring diseases and/or with concomitant immuno↓ drugs
- So far, less evidence that rituximab in monotherapy favors PML
- Efalizumab: high risk of PML
- Alemtuzumab and anti-TNFα: little evidence that they trigger PML