



# Evidence about plasma exchange in natalizumab related PML

### Ralf Gold Neurologische Klinik St. Josef Hospital, Klinikum der Ruhr-Universität Bochum

- An opportunistic infection is an infection caused by <u>pathogens</u> (bacterial, viral, fungal or protozoan) that usually do not cause disease in a healthy host, i.e. one with a healthy immune system.
   A <u>compromised immune system</u>, however, presents an "opportunity" for the pathogen to infect. (WIKIPEDIA)
- CDC/WHO: mycobacteria tuberculosis, toxoploame condide LSV LC virus
   Morbidity and Mortality Weekly Report

 www.cdc.gov/mmwr

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### Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

# Putative mechanism of action of Natalizumab (IgG4)



## Key questions about PLEX

 Evidence that natalizumab causes immune suppression ... and that this is reversible by PLEX ?

2. Comparison of PML natural outcomes with PLEX regimens

3. Immunoadsorption for more specifical removal than the standard plasma exchange ?

### Natalizumab: PML-incidence indicates Immune Compromise: The incidence is related to treatment duration



\*Yousry TA, et al. N Engl J Med. 2006;354:924-933.

Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab. The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment duration are calculated based on TYSABRI exposure through June 30, 2011 and 145 confirmed cases as of July 5, 2011. The incidence for each time period is calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g. for ≥24 infusions all PML cases diagnosed with exposure of 24 infusions or more divided by the total number of patients exposed to at least 24 infusions). Biogen Idec, data on file.

### Efalizumab PML

- Adhesion molecules and PML...
- Why not other brain infections ?
- Why not MS PML with cytostatic mitoxantrone and cyclophosphamide..
- Reduced CNS surveillance vs peripheral suppression....what do the clinical observations tell us about the underlying biology?

### Is it reversed by PLEX?

- IRIS says "yes"
- The fact that IRIS occurs 3-5 weeks post plex and 12ish weeks without PLeX, says "yes".
- at least Cylex data support for restitution of peripheral immune activity



### Functional Energetics of CD4<sup>+</sup>-Cellular Immunity in Monoclonal Antibody-Associated Progressive Multifocal Leukoencephalopathy in Autoimmune Disorders

#### Aiden Haghikia<sup>1</sup>, Moritz Perrech<sup>1</sup>, Bartosz Pula<sup>1</sup>, Sabrina Ruhrmann<sup>1</sup>, Anja Potthoff<sup>2</sup>, Norbert H. Brockmeyer<sup>2</sup>, Susan Goelz<sup>3</sup>, Heinz Wiendl<sup>4</sup>, Hans Lindå<sup>5</sup>, Tjalf Ziemssen<sup>6</sup>, Sergio E. Baranzini<sup>7</sup>, Tor-Björn Käll<sup>8</sup>, Dietmar Bengel<sup>9</sup>, Tomas Olsson<sup>10</sup>, Ralf Gold<sup>1</sup>, Andrew Chan<sup>1</sup>\*

1 Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany, 2 Department of Dermatology and HIV Competence Center, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany, 3 Biogen Idec, Cambridge, Massachusetts, United States of America, 4 Department of Neurology, Westfälische Wilhelms-Universität Münster, Münster, Germany, 5 Neurology Unit, Department of Medicine, Karolinska Institute, Danderyd Hospital, Stockholm, Sweden, 6 Department of Neurology, Technical University, Dresden, Germany, 7 Department of Neurology at the University of California San Francisco, San Francisco, California, United States of America, 8 Clinic of Internal Medicine Södersjukhuset, Stockholm, Sweden, 9 Neurologic Clinic, Oberschwabenklinik, Ravensburg, Germany, 10 Department of Neurology, Karolinska Hospital, Stockholm, Sweden

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### **HIV patients and ATP**



### PML under natalizumab – European cases



# Cylex data in PML in mAb associated opportunistic CNS infections



Biogen Idec Data on file. \* basierend auf 33 von 79 Fällen zum 2. Dezember 2010

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\*Basierend auf 68 PML-Fällen bis September 2010. 42 der 68 Patients hatten MRT-Scans/Berichte, die zum Zeitpunkt der PML-Diagnose Vorliegen oder Fehlen von KM-Aufnahme erwähnten.

# Approaches to eliminate Tysabri

### The forced approach..

 Plasmapheresis procedures

via PLEX – US way

via Immunadsorption

- European option...

29/145 patients postmark. usage died (20%) The natural way..

- After infusion 100 µg/ml
- 4 weeks later: 10 µg/ml
- Wait another 2 mths for complete elimination..

2/3 patients in pivotal studies died

 1 Dutch patient had spontaneous mild course
 Vennegoor - Polman <u>Neurology</u>.
 2011 Feb 8;76(6):574-6.

### Functional Status in PML Survivors with at Least 6 Months of Follow-up Time

	Survivors (n=38)				
	Mild Disability	Moderate Disability	Severe Disability		
Functional Status	(Karnofsky Score = 80–100)	(Karnofsky Score = 50–70)	(Karnofsky Score = 10–40)		
No. (%) of patients at clinical status and ≥6 months since PML diagnosis	5 (13%)	19 (50%)	14 (37%)		

- Majority of patients with severe disability (12/14, 86%) had Karnofsky scores of 40, which is at the interface between moderate and severe disability
- MS can contribute to lower Karnofsky scores, and Karnofsky scores pre-PML/pre-natalizumab were reported for very few patients (n=7). The average change in Karnofsky score attributable to PML for these 7 patients was 26

### MRI Images at PML Diagnosis, Immune Reconstitution Inflammatory Syndrome (IRIS), and After IRIS Treatment<sup>1</sup>



Serial axial postcontrast T1-weighted (A–C) and T2-weighted (D–F) MRI images of the brain at PML diagnosis (A and D), in the IRIS phase (B and E), and after treatment (C and F)

1. Schröder A et al. Arch Neurol. 2010;67:1391-1394.

### **Tysabri-treated PML Cases**

### Frequency of IRIS is Similar in Patients With or Without PLEX/IA

• As of 28-Jan-2011 with 93 confirmed PML cases, the majority of patients (84/93, 90%) underwent accelerated removal of Tysabri from the circulation by PLEX and/or

Treatment Received (PLEX and/or IA )	Number of Confirmed PML patients (N=93)		Number/percent of patients who developed IRIS	
PLEX alone	76	- 84 patients		-
IA alone	4			56/84 (67%)*
PLEX and IA	4	,		, 
NO PLEX or IA	4			4/4 (100%)
Unknown status	5			4/5 (80%)

\* 2 patients (2/84, 2%) did not develop IRIS and the occurrence of IRIS was either not reported or unknown for 26 patients (26/84, 31%)

- IRIS usually occurred days to several weeks after PLEX/IA
- In patients who did not receive PLEX/IA, IRIS usually occurred approximately 3
  months after the last dose of Tysabri
- Most patients were treated with corticosteroids for IRIS (or IRIS prophylaxis) 73/93, 78%;

7 patients were not treated with corticosteroids and it was unknown if corticosteroids

From www.bloodjournal.org at RUHR-UNIVERSITAET BOCHUM on October 8, 2009. For personal use only. CLINICAL TRIALS AND OBSERVATIONS

Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project

Kenne John I Julie I Kenji I and C 'Sitema Medicin of Medi Centre I Univers Hemato NY; 12V

so far all rituxan associated JC infections had an unfavorable outcome Suggesting that an intact peripheral immune system is important for good outcomes. We just need to get the cells back into the brain!!

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<sup>19</sup>Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia; Departments of <sup>14</sup>Neurological Surgery and <sup>15</sup>Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL; <sup>16</sup>Kansas City Cancer Center, MO; <sup>17</sup>Tulane Medical School, New Orleans, LA; <sup>10</sup>Laboratory of Molecular Medicine and Neuroscience, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; and <sup>10</sup>Veterans Administration Center for the Management of Complex Chronic Conditions, Jesse Brown VAMC, Chicago, IL



07/10

09/10



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### **Plasmapheresis**

Plasmapheresis is a form of therapy to separate plasma from blood, remove pathogenic substances from plasma, either replace with substitution fluid or purify. Plasmapheresis is indicated in collagen disease, autoimmune disease





Centrifugation and membrane separation techniques are used for plasma separation. There several types of membrane plasmapheresis, including: <u>plasma exchange (PE)</u>, immunoadsorption (IA).

In PE, plasma separated with a plasma separator is discarded and replaced with the same volume of fresh frozen plasma (FFP) or albumin solution.

In PA, plasma separated with a plasma separator flows into a plasma adsorption column. Pathogenic substances are adsorbed and removed due to affinity between ligands and pathogenic substances. The advantage of this method is that no substitution fluid is required.

IA is a subcategory of PA because it follows the same method. It is referred to as IA when the adsorption column selectively adsorbs immune complexes and auto-antibodies.

### **Plasmapheresis to remove natalizumab**



Kathri et al. Neurology 2009:72:402-408

#### BRIEF REPORT

The plasma-exchange treatments significantly decreased the concentration of natalizumab in the patient's serum, from 14.4  $\mu$ g per milliliter before treatment to 8.7  $\mu$ g per milliliter after the second treatment and 5.5  $\mu$ g per milliliter after the third treatment.

Caroline Ryschkewitsch, B.S., Johan Berg, M.D., Tomas Olsson, M.D., Ph.D., and Claes Martin, M.D., Ph.D.

N Engl J Med 2009;361:1081-7.

The NEW ENGLAND JOURNAL of MEDICINE

An analysis of serum obtained 4 days before 1 PE-3 imm.adsorp. revealed a natalizumab level of 10.8  $\mu$ g per milliliter, and analysis of serum obtained 2 days after immunoadsorption showed that the natalizumab concentration was below detection level (0.25  $\mu$ g/ml).

Werner Wenning, M.D., Aiden Haghikia, M.D., Jörg Laubenberger, M.D., David B. Clifford, M.D., Peter F. Behrens, M.D., Andrew Chan, M.D., and Ralf Gold, M.D.

N Engl J Med 2009;361:1075-80.

### Another example of Immunoadsorption (Kleiter et al. Mult Scler 2010 – natalizumab by Dr Goelz)



# Summary 'to PLEX or not to PLEX...'

- No controlled studies available...
- Indirect evidence for plasma exchange: immune parameters, clinical outcome
- Maybe even more specific for IgG4 removal: immunoadsorption columns

Thanks to Drs. Kerstin Hellwig, Susan Goelz, , Ingo Kleiter, Alexandra Schroeder, Sandra Richman

### Active management of IRIS !!

- MRI monitoring of brain swelling starting 3-4 weeks after removal of natalizumab (via PE etc)
- Repeated pulses of methylprednisolone (3 days a 1000mg), even forced immunosuppression
- Osmotherapeutic agents
- Anti viral therapy with mefloquine and mirtazapine to be continued
- Critical denominator of final outcome !