18TH STATE OF THE ART

SYMPOSIUM of the Swiss Multiple Sclerosis Society www.multiplesklerose.ch

MEETING REPORT
SATURDAY, JANUARY 30TH, 2016

KKL, Luzern, Culture and Convention Centre

MS Swiss Multiple Sclerosis Society

supports research

GENERAL INFORMATION

Venue
KKL Luzern, Europaplatz 1, CH-6005 Luzern
www.kkl-luzern.ch

Programme committee
Britta Engelhardt, Bern; Claudio Gobbi, Lugano;
Tobias Derfuss, Basel; Christian Kamm, Bern;
Patrice Lalive, Geneva; Renaud Du Pasquier, Lausanne

Organisation
Swiss MS Society and its Scientifc Advisory Board

Contact
Swiss MS Society, Josefstrasse 129, CH-8031 Zürich
symposium@multiplesklerose.ch
www.ms-state-of-the-art.ch

MS Swiss Multiple Sclerosis Society
supports research

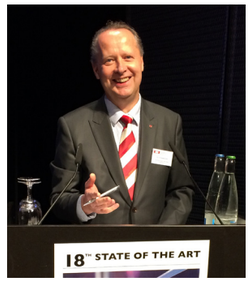
MEETING REPORT

TABLE OF CONTENTS

AGENDA

TIME	TOPIC	SPEAKER
10.00 – 10.10	Welcome from the Swiss MS Society	Prof. Britta Engelhardt, Bern Dr Christoph Lotter, Zürich
10.10 – 10.40	Pregnancy and Oestrogens	PD Dr Kerstin Hellwig, Bochum
10.40 – 11.10	Lifestyle Factors in MS – Interactions with MS Risk Genes	Prof. Tomas Olsson, Stockholm
11.10 – 11.40	MS and Vaccinations	Dr Matthias Mehling, Basel
11.40 – 12.10	**Coffee Break**	
12.10 – 12.35	Environmental Factors – Vitamin D	Dr Joost Smolders, Nijmegen
12.35 – 12.50	Swiss MS Registry and Swiss Cohort Study	Dr Viktor von Wyl, Zürich and PD Dr Jens Kuhle, Basel
12.50 – 13.15	New Drugs and changing Treatment Algorithms	Prof. Ludwig Kappos, Basel
13.15 – 14.15	**Lunch**	
14.15 – 15.00	Workshop A – Impact of PML Risk in the Treatment of MS	Prof. Tobias Derfuss, Basel Dr Christian Kamm, Bern
	Workshop B – Biomarkers in MS	Prof. Andrew Chan, Bern PD Dr Jens Kuhle, Basel
15.00 - 15.20	**Coffee Break**	
15.20 – 16.05	Workshop C – Neuroprotection: What is in the Pipeline?	Prof. Roland Martin, Zürich Prof. Caroline Pot, Lausanne
	Workshop D – Brain Atrophy in Clinical Practice: Useful or Nonsense	PD Dr Cristina Granziera, Lausanne Prof. Sven Schippling, Zürich
16.05	**Farewell Apero**	

WELCOME FROM THE SWISS MS SOCIETY



CHRISTOPH LOTTER
Zürich, Switzerland

BRITTA ENGELHARDT
Bern, Switzerland

Dr Lotter welcomed all attendees to the 18th State of the Art Symposium on behalf of the Swiss Multiple Sclerosis Society. Recent epidemiological studies demonstrate that in addition to genetic factors environmental factors influence susceptibility to Multiple Sclerosis (MS) and additionally influence the disease course. Therefore, the 18th State of the Art Symposium focused on delivering the latest research to aid patient care and further clinical practice.

The President of the Scientific Advisory Board, Prof. Engelhardt, officially opened the symposium on the impact of comorbidities and environmental factors on the onset and progression of MS. Internationally well-known MS experts presented recent advances in the field. In addition, there was an update on the Swiss MS Registry and the Swiss MS Cohort Study and a presentation on changing MS treatment algorithms to incorporate new and emerging drugs. Finally, two sets of parallel workshops allowed attendees to discuss how to translate research to daily clinical practice.

The State of the Art Symposium is one of the most prominent meetings among more than 100 events organised by the Society every year. In addition to reaching to more than 11,000 people with the latest information regarding living with MS in Switzerland, the Swiss MS Society also provides financial aid to people lacking insurance coverage, and participates in the advancement of science by funding numerous research projects. Thanks to a careful balance between private donations (>80%), public funding (15%) and industry support (3%), the financial independence of the MS Society is guaranteed, thus allowing absolute fairness and neutrality in all communications with the MS community. These factors mean that clinicians receive top-quality education that in turn benefits the lives of people with MS and their families.

The MS Society was founded in 1959. Today it has 15,000 members and 75,000 donors. Three centres are in operation: in Zürich, Lausanne and Lugano-Massagno, with 55 employees, 50 regional groups and 1300 volunteers. The Scientific Advisory Board is an independent institution that supports the MS Society in all medical and research aspects (link between the society and the research community, answering specific research questions etc.). In 2015, research spending increased more than 20% — meaning the MS Society looks forward to a future in which independent, cutting-edge research helps the MS community to better understand and treat MS.

MEETING REPORT

PREGNANCY AND OESTROGENS

KERSTIN HELLWIG
Bochum, Germany

During the first presentation of the day, Dr Hellwig reviewed the effects of pregnancy and oestrogen levels on MS susceptibility and outcomes. Her aim was to provide information that clinicians can use to answer the most common questions asked by patients.

MS is known to principally affect young women in their reproductive age. The reasons for the uneven distribution of MS prevalence over the two genders are still poorly understood. In the first part of her presentation, Dr Hellwig presented potential factors that could explain an increased susceptibility to MS in women. Interestingly, the risk of developing MS seems to have increased during the last few decades in females only, a timespan that is too short to allow genetic factors to be the sole explanation for such increase. Environmental factors may therefore play a role too.

Currently, women have fewer children than ever and their first birth occurs at an ever later age. As a consequence, occidental women undergo approximately 10 times more menstrual cycles over their lifespan compared with ancient and other tribal lifestyles. This extreme change in reproductive lifestyle may have an effect on MS risk. Another environmental factor that is often cited is the exposure to exogenous hormones. Dr Hellwig presented a study she conducted between 2008 and 2011 in Pasadena, California, to investigate the role of oral contraception on MS risk. Contrary to what experts would have expected, the pill did not exert a protective role against the risk of developing MS, and while progestin-only contraceptives did not increase the risk, levonorgestrel-containing contraceptives were associated with a significant risk increase. In the same study, a higher rate of MS and earlier onset of symptoms in obese patients was confirmed, especially in those with high bodyweight during childhood and adolescence.

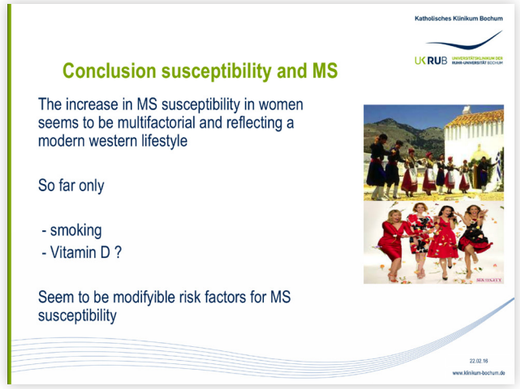
Dr Hellwig concluded that the increase in MS susceptibility in women seems to be multifactorial and to reflect a modern western lifestyle. The only modifiable risk factors associated with MS seem to be smoking, and potentially vitamin D intake. Oral contraception should be advised to all young women despite the marginal risk contribution to developing MS.

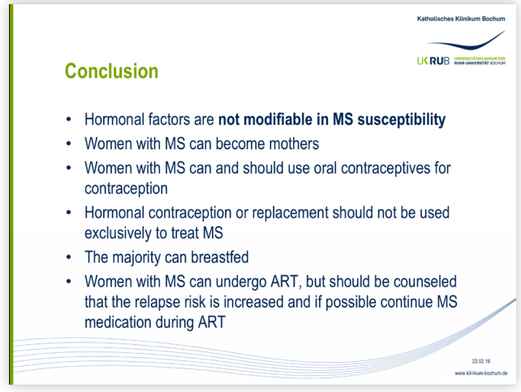
In the second half of her presentation, Dr Hellwig presented the effect of hormonal factors on the course and prognosis of MS. She showed that during pregnancy, an 80% reduction in the rate of MS relapses is observed, in particular during the third trimester. Unpublished results were shown of a clinical study investigating the potential of hormonal replacement that imitates pregnancy to counter the high relapse rates usually observed postpartum. Unfortunately, no reduction in disease activity was observed, showing that it is very difficult to imitate natural pregnancy with exogenous hormones without significantly increasing the risks of thromboembolism and cancer.

When administered to women with MS in combination with disease-modifying therapies, estriol – the hormone produced exclusively during pregnancy – showed a protective effect against relapse in two independent studies. However, the observed decrease in clinical symptoms was not mirrored by development of fewer lesions in the central nervous system (CNS), and more research is needed to confirm any conclusions.

Dr Hellwig reviewed the current literature on the use of artificial reproductive techniques (and associated hormonal therapies) and concluded that it can be attempted in patients with MS, although unsuccessful attempts are known to increase the risk of relapses. GnRH agonists – hormones used to control ovulation prior to in vitro fertilisation – should be avoided, but any MS medication other than Aubagio® (teriflunomid) and Gilenya® (fingolimod) should be continued.

In conclusion, when asked whether pregnancy will increase the rate of disease progression in a patient with MS, clinicians should respond that the effect of a pregnancy (or multiple pregnancies!) will most probably be neutral; neither deleterious nor protective.





MEETING REPORT

LIFESTYLE FACTORS IN MS - INTERACTIONS WITH MS RISK GENES

TOMAS OLSSON
Stockholm, Sweden

> *"Traditionally, epidemiologists have only collected data about risk factors and geneticists only took blood samples. But it is important to do both and combine the knowledge."*
>
> *Prof. T. Olsson*

MS is often characterised by an unpredictable, variable disease course. Periods with symptomatic flares and disease exacerbation are followed by intervals of remission. It is difficult to identify the triggers of MS, because these occur long before the clinical onset of the disease. In addition, initial symptoms are often overlooked as they may be brief and mild. Precise knowledge of the factors that cause and drive MS is required to provide prevention and to develop new efficacious, selective therapies.

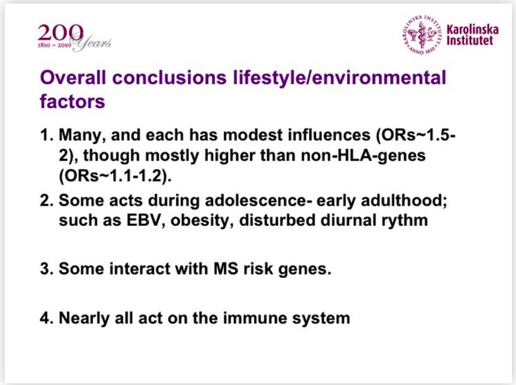
Genetic predisposition

It has long been known that MS has a genetic basis. People with a family history of MS bear an increased risk of developing MS. This risk is conveyed by specific variants of normal genes, so called risk genes. The best studied and strongest risk genes encode for proteins on the surface of cells that are responsible for regulating the immune system – the human leukocyte antigen (HLA) system. Over the last two decades, almost 200 additional risk genes with lower risk associations have been identified; those for which the function is known are all related to immunity. This fact strongly supports that MS is driven by inflammation and is not secondary to an unknown cause of neurodegeneration. Investigation of these factors may broaden our understanding of how MS develops and may prove useful in the development of newer therapies.

Influence of environmental factors

The genetic predisposition only accounts for a part of the risk to develop MS – roughly 15–20%, and environmental factors play an important role too. More and more factors are found, for example smoking, exposure to organic solvents, Epstein-Barr virus (EBV) infection, low sunlight exposure, reduced vitamin D levels, or obesity during adolescence.

Importantly, both risk genes and environmental factors alone only increase the risk for MS modestly. For example, smoking, one of the strongest environmental factors, almost doubles the risk of MS. However, the risk to get the disease becomes much higher if a person has the MS-predisposing risk gene variant and is exposed to negative environmental factors.



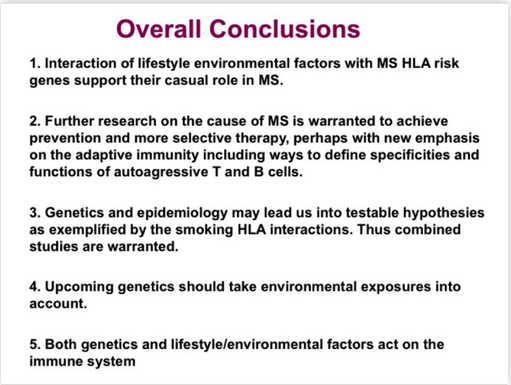
Interaction genes / environment

The genetic and epidemiological fields have operated very separately for a long time. More than ten years ago, Prof. Olsson and others started to combine environmental and genetic studies. Large data sets about genetic factors as well as life style and environmental characteristics (i.e. smoking, alcohol habits, vaccination history, sunlight exposure, etc.) were collected from thousands of MS patients and healthy individuals in a Swedish Registry.

In the studies, interactions of environmental factor with the strongest risk genes from the HLA group were used (HLA DRB1*15:01 and HLA A2). The risk of developing MS was substantially increased among smokers with both genetic risk factors compared with non-smokers with neither of these factors. Similar results were seen with organic solvent exposure, passive smoking, EBV infection, and obesity at age 20, while there were no interactions between sun exposure habits / vitamin D levels, night shift work and HLA MS risk genes. Interestingly, oral tobacco does not increase the MS risk. This suggests that the effect seen with smoking is caused by lung irritation and not due to nicotine, which fits with the negative risk associated with solvent exposure. These immune reactions will be important to study.

How to minimise MS risk

Being a multifactorial disease, it is impossible to predict the individual risk of MS and most factors cannot not be influenced. Based on the presented data, Prof. Olsson strongly recommended not to smoke, or to quit smoking and to avoid obesity, especially before the age of 20. To gain more insight into how MS develops, upcoming studies of MS genetics should take lifestyle / environmental factors into account.



MEETING REPORT

MS AND VACCINATIONS

MATTHIAS MEHLING
Basel, Switzerland

The internet is populated with multiple reports showing vaccines to cause chronic immune system dysregulations or to trigger autoimmunity. In response, clinicians are frequently asked by their patients with MS whether vaccination induces MS, if it can trigger disease relapses, or if MS medication can preclude vaccination response. As the mechanisms leading to MS and those involved in vaccine response heavily involve the immune system, these questions are perfectly legitimate and deserve our attention. In his presentation, Dr Mehling examined closely the most recent medical literature on the topic in an attempt to provide unequivocal answers to these important questions.

Can vaccines induce MS?

The risk to develop MS after immunisation with specific vaccines has been studied thoroughly. Clinical studies have demonstrated that none of the vaccines composed of an innocuous subunit (rather than attenuated of inactivated pathogens) increases the probability or developing MS: the vaccines against diphtheria, tetanus, pneumonia, meningitis, hepatitis B, human papillomavirus, whooping cough, diphtheria, and the flu are safe.

Likewise, there is strong evidence demonstrating that the following vaccines containing attenuated or inactivated pathogens do not cause MS onset: poliomyelitis, hepatitis A, measles, mumps, rubella, varicella and tuberculosis.

Even though vaccination does not increase the overall likelihood of developing MS in the course of life, it might potentially impact on the time point of disease onset in people who develop MS.

Finally, a preliminary study of the BCG vaccine (against tuberculosis) showed a protective effect in people with MS: in vaccinated patients, fewer lesions were recorded by magnetic resonance imaging (MRI) than in non-vaccinated ones. Vaccination would in this case reduce the risk of developing the clinical symptoms characteristic of MS.

Can vaccines trigger MS relapses?

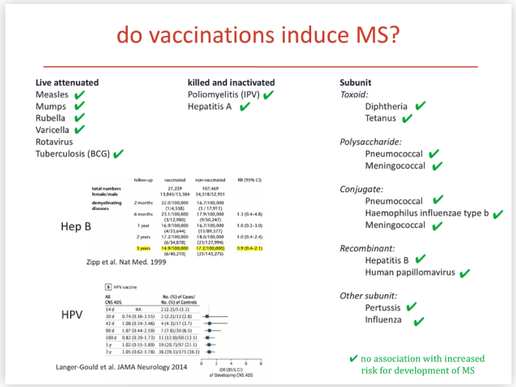
A large clinical study that studied 643 patients with MS in 6 different European centres, showed that vaccination against tetanus, hepatitis B, and influenza alone or in combination did not increase the risk of relapse. One exception may be the live attenuated vaccine against yellow fever, which has been reported in small case series to increase the risk of relapses. Therefore, the decision with regards to yellow fever vaccination has to be carefully balanced. Dr Mehling reminded the audience that virus infections increase the risk of relapse far more than any vaccine.

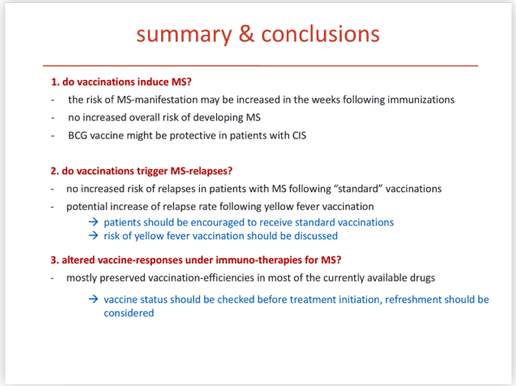
Can MS therapies influence response to vaccination?

Among all disease modifying therapies (DMTs), the only medication used to slow the course of MS that reduces the magnitude of vaccine response is fingolimod. However, although of smaller magnitude, patients treated with fingolimod were still able to mount an immune response to vaccination.

The results of a clinical trial studying the vaccination response in people with MS receiving dimethyl fumarate are expected later this year.

In conclusion, Dr Mehling encourages the general population to get vaccinated. Likewise, patients with MS should not fear vaccination. No association is found with additional relapses and most MS therapies do not interfere with the efficacy of vaccines.





ENVIRONMENTAL FACTORS – VITAMIN D

JOOST SMOLDERS
Nijmegen, The Netherlands

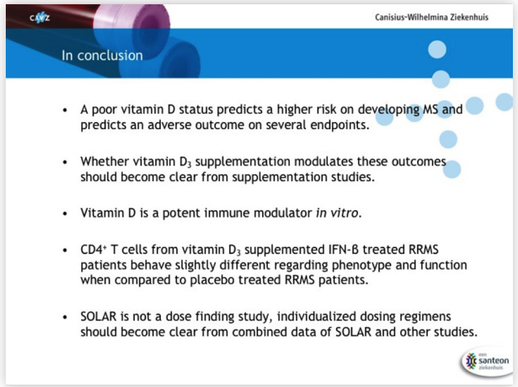
"It is good for people with MS to know their vitamin D status. In case the status is so low that their bone health may be compromised, it is beneficial to supplement vitamin D. Whether or not supplementation also results in improved clinical outcomes is not known yet. But we are working very hard to gather data to answer this question."

Dr J. Smolders

Sunlight is our main source of vitamin D. When the skin is exposed to the ultraviolet radiation of the sun, it produces vitamin D3. We can also take up vitamin D through our diet by eating fish, egg yolks and mushrooms, for example. In its active form (1,25-dihydroxyvitamin D), vitamin D is capable of influencing the metabolism of many organs of our body by interacting with a variety of genes. Examples are the small intestine where it increases calcium absorption. Vitamin D also travels to the skeleton to mobilise calcium from the bones, or to the brain where it acts as a neuroprotectant, thereby playing a role as a modulator of brain function and development.

Low vitamin D levels are associated with an increased risk of developing MS. The most important findings are that patients with early relapsing remitting MS (RRMS) and a poor vitamin D status do worse regarding several crucial disease outcomes. They have more frequent relapses and a more active disease can be evidenced by MRI. In addition, low vitamin D levels are also associated with increased disability. Patients with a rapid transition towards progressive MS displayed lower vitamin D levels at diagnosis than patients with a prolonged RRMS phase. This may suggest that vitamin D could act as a disease modifier, however it is not yet clear whether low vitamin D levels are a consequence of active MS or a causative factor.

In vitro and experimental models showed that the active form of vitamin D plays an important role in the adaptive immune response. It is upregulated upon immune reactions and seems to act as a "handbrake" by preventing immune cells from going out of control. This modulatory



role that seems to take place in the lymph nodes and the CNS could be very important in people with MS. It is possible that vitamin D does not only play a regulatory role in these experiments, but also in patients with MS. This would explain the correlation seen between vitamin D status and disease outcomes

So far, it has not been shown that supplementation with vitamin D can improve immunological outcomes. It would be very exciting if the disease course of MS could be influenced by such an easily manageable intervention. Clinical trials to clarify the effect of supplementation are ongoing and results may provide more clarity in the near future.

SWISS MS REGISTRY AND SWISS MS COHORT STUDY

VIKTOR VON WYL
Zürich, Switzerland

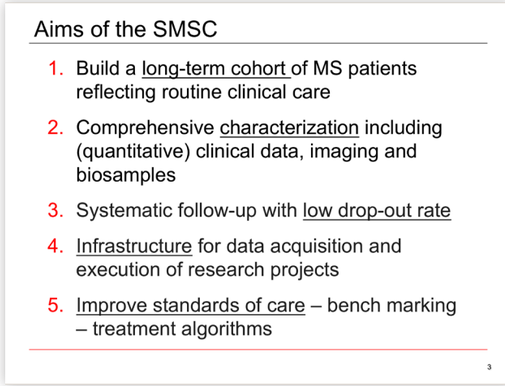
JENS KUHLE
Basel, Switzerland

Together, the Swiss MS Registry (SMSR) and the Swiss MS Cohort Study (SMSC) create a very unique study base for highly innovative national and international MS research.

Dr Kuhle explained – on behalf of the 7 participating clinics – that the SMSC is a clinic-based, observational study that started recruiting well-documented, clinically confirmed MS cases in June 2012. The objective is to characterise thoroughly the routine clinical care in a long-term cohort of MS patients by analysing quantitative clinical data, imaging and biosamples. The resulting real-life data acquisition infrastructure will provide an opportunity for executing research projects that are not bound to the limitations of Phase III studies, with the overall aim of improving treatment algorithms and standard of care of this complex inflammatory and neurodegenerative disease.

So far, 960 patients were recruited; owing to a systematic follow-up approach, a very low drop-out rate was recorded over a median follow-up of 2 years. Initial data (in patients with at least two recorded visits) allows extracting information on the progression rate of disability via EDSS scores rated by certified examiners, quantifying relapse numbers and frequency, and observing the conversion of RRMS into progressive MS. In addition, the SMSC allows monitoring of the evolution of disease-modifying therapies used over time and thus detecting changes in the treatment algorithms. Finally, a biobank containing >70,000 blood samples and >1,500 MRI scans is available.

Dr Kuhle concluded by stating that, although still young, the SMSC is ready to start producing results, and

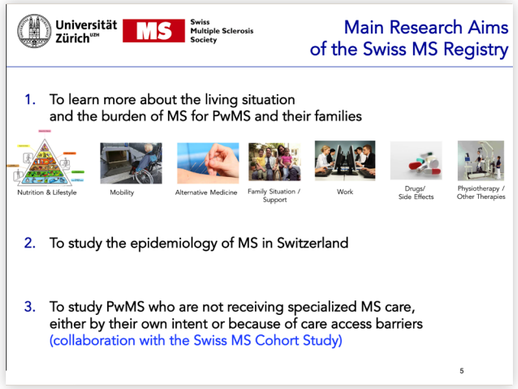


statistical analysis of the data should be initiated shortly. He encouraged all attendees who would have ideas on statistical analyses of interest to get in contact with one of the involved centres and establish a collaboration or run a nested research project.

Dr von Wyl presented the sibling study – the SMSR – by clarifying that the most important difference between the two studies is the patient population that is enrolled. While the SMSC focuses on well-characterised patients who regularly visit one of the participating clinics, the SMSR is more inclusive, which allows enrolling people living with MS who are typically excluded from clinical research (i.e. people with severe disabilities, people not receiving care at MS centres, etc.). Enrolment will start in June 2016, and interactive tools such as online voting and feedback systems, patient diaries, and discussion forums will be offered to maintain the engagement of the MS community with the SMSR. A broad range of

topics will be monitored via surveys, including nutrition, physiotherapy, and mental health, and clinical information will be obtained where possible by medical record abstraction. One of the important objectives of the SMSR is to provide information tailored to people with MS, in addition to serving as a database for clinical research.

The close partnership between the the SMSC and the SMSR will ensure a maximum of synergy, and is expected to provide comprehensive, high quality data and a unique platform for nested studies.



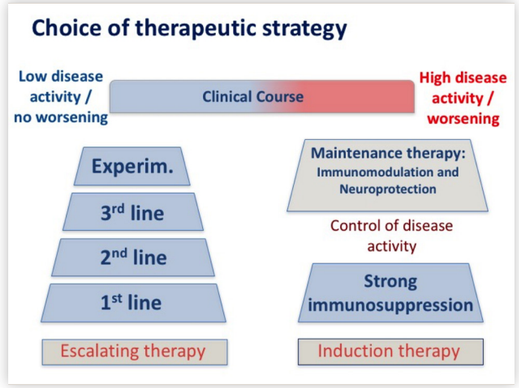
NEW DRUGS AND CHANGING TREATMENT ALGORITHMS

LUDWIG KAPPOS
Basel, Switzerland

In the concluding presentation of the morning session, Prof. Kappos presented an overview of the recent developments concerning MS treatment. In the last few years, several new compounds to treat RRMS and clinically isolated syndrome (CIS) have been approved by health authorities all over the world. With extensive research activities ongoing, our understanding about the immune system involvement in the disease course of MS is increasing significantly, and more new therapeutics are expected to become available. The novel treatment options include both oral treatments and monoclonal antibodies that are not only tolerated better, but some are also more effective in direct head-to-head comparisons with well-established medications.

As a consequence of the growing number of treatment options, the treatment landscape is becoming more and more complex. To be able to select compounds based on clear-cut data, a large number of clinical trials directly comparing one drug to another would be required; however, this scenario is highly unlikely. Nevertheless, the new therapeutics have to be integrated into the daily clinical practice and physicians need guidelines and recommendations on which compounds are best suited to their patients. One main challenge is to balance the risks, for example due to side effects, and benefits, e.g. absence of relapses or delayed disease progression, that treatments mean for the individual patients, both in the short and long run. This core challenge always involves an assessment of whether a patient is at a high risk of developping disability and therefore requires an aggressive treatment approach, or if a safer approach can be chosen and treatment can still be escalated if necessary without major negative effects.

New risk stratification models are being developed and evaluated that may better predict which patients will respond to a given treatment. While the management of MS remains a highly challenging field, our understanding of the underlying disease biology is improving and more long-term treatment data is emerging. These data and novel treatment options will certainly improve the outlook for people with MS.



MEETING REPORT

WORKSHOP A – IMPACT OF PML RISK IN THE TREATMENT OF MS

TOBIAS DERFUSS
Basel, Switzerland

CHRISTIAN KAMM
Bern, Switzerland

Progressive multifocal leukoencephalopathy (PML) is a severe infection of the CNS that is very difficult to treat and may cause death or severe disability. Because some DMTs in MS increase the risk of PML, this has been one of the most discussed topics among clinicians and researchers in the field.

Prof. Derfuss opened this workshop session by explaining the mechanisms that lead to PML, the most frequent symptoms, and the tests needed for diagnosis.

PML is caused by reactivation of the John Cunningham virus (JCV) in immunosuppressed individuals. In Switzerland, over 50% of the population are infected with JCV during childhood or adolescence. Infected individuals carry the virus their entire lives. In healthy individuals, the virus migrates to the kidneys, spleen, bone marrow and maybe even to the brain. Reactivation does normally not cause any symptoms. In patients who are immunosuppressed, JCV is activated, becomes capable of infecting nerve cells, and migrates into the brain. There, it results in demyelination of brain cells and degradation of supporting cells important for brain function – astrocytes and oligodendrocytes.

The initial symptoms of PML are often mistaken for a relapse of MS. However, signs such as visual field deficits, speech difficulties or seizures are clearly indicative of PML. Particular attention should be paid to patients who present relapse symptoms while receiving Tysabri® (natalizumab) as they have a lower risk of a MS relapse and a higher risk of developing PML.

When clinical signs of PML are suspected, doctors should look at MRI scans and assess the need for more invasive tests to confirm PML diagnosis. For confirmation, the levels of JCV-DNA in the cerebrospinal fluid (CSF) of patients are usually measured by PCR, but only specialised laboratories provide trustworthy results. More recently, the levels of JCV-specific antibodies in CSF have been used for diagnosis with a reliability that remains to be confirmed. During his presentation, Prof. Derfuss encouraged all clinicians to be persistent with diagnosis confirmation when PML is suspected – resorting to brain biopsy is acceptable for PML confirmation.

During the second part of this workshop, Dr Kamm elaborated on the risk of PML associated with 3 DMTs used in MS.

Overall, PML is observed in 4 out of 1000 patients receiving Tysabri®. In order to advise this treatment option exclusively to the patients with the lowest probability of developing PML, the risk was calculated in different subgroups of people living with MS. Any risk superior to 1.5 in 1,000 should encourage the clinician to consider treatment discontinuation.

Individuals who have never been in contact with JCV (i.e. in whom no JCV-specific antibodies could be detected) have a PML risk low enough to encourage Tysabri® prescription. Among patients who have been in contact with the virus, having received immunosuppressive therapy in the past increases the PML odds. Another factor known to correlate with PML frequency is the duration of Tysabri® treatment. Further refinement of the decision of whether to prescribe/continue Tysabri® therapy is based on the "level" of JCV infection (i.e. anti-JCV antibody index).

In addition to risk-based Tysabri® prescription, regular monitoring of clinical signs decreases the odds of developing PML. MRI scans are recommended every 6 months and should be accompanied with tests to confirm the lack or level of anti-JCV antibodies.

Tecfidera® (dimethyl fumarate) and Gilenya®(fingolimod) are also believed to increase the probability of developing PML, although to date, only 4 and 5 cases were confirmed, respectively. Often in these patients, PML was accompanied with lymphopenia – low levels of one type of white blood cells. Dr Kamm suggested that treatment discontinuation should be considered for those who develop lymphopenia while receiving Tecfidera®. For Gilenya® there is no clear lymphocyte cut-off that correlates with an increased risk for PML. Dr Kamm concluded that more data will be needed to define a realistic treatment algorithm.

MEETING REPORT

WORKSHOP B – BIOMARKERS IN MS

ANDREW CHAN
Bochum, Germany
Bern, Switzerland

JENS KUHLE
Basel, Switzerland

Biological markers, or short biomarkers, are measurable characteristics that can be tested to assess normal biological processes or to indicate the presence and severity of a particular disease. Biomarkers are also used to measure whether (and to what extent) a given therapeutic intervention is working or how likely undesired side effects are to occur. For example, an increased blood glucose level is a well-known diagnostic biomarker of diabetes.

The study of MS would benefit particularly from the use of specific biomarkers, because the disease manifestation is very heterogeneous between individual patients. Biomarkers could assist with diagnosis, prediction of disease course, or identification of response outcome to treatments as well as potential adverse drug reactions.

Even though extensive effort has been put into the development of biomarkers for MS, their validation and clinical application is still limited due to the high clinical and pathophysiological complexity of the disease. Only few biomarkers are currently aiding in a clinically meaningful fashion. However, a large number of experimental biomarkers are being studied and might be integrated into routine clinical practice in the years to come.

During the workshop the speakers gave an overview of the importance of established biomarkers for clinical practice and presented research data on biomarkers in development.

Diagnostic biomarkers

Despite the well-established diagnostic procedure for MS, diagnostic biomarkers could be crucial for diagnosis confirmation and could help better understand the disease pathogenesis. Aquaporin-4 antibody proved to be valuable in distinguishing between MS and another demyelinating disease named neuromyelitis optica (NMO). The majority of NMO patients (approximately 70%) have detectable blood levels of the antibody, while they are absent in MS. IL-6 may be another marker for NMO, but additional research efforts are required to investigate its role in the disease aetiology.

Biomarkers to assess treatment response

Intense research efforts are also ongoing to discover clinically applicable biomarkers to assess early on if treatments are effective. High levels of the protein chitinase 3-like 1 and neurofilaments were shown be correlated with increased severity of MS in several studies and may help to monitor therapeutic decisions in the future.

Markers to assess risk of developing undesirable side effects

Biomarkers are investigated to stratify the risk of developing treatment-associated adverse events. Dr Chan presented practical recommendations on how the number of lymphocytes (a specific type of white blood cells) may be used to gauge the risk of PML in people who receive dimethyl fumarate immunomodulatory treatment. As a second example, the PML risk in patients receiving natalizumab was discussed (also see Workshop A).

In summary, extensive research is ongoing to identify clinically relevant biomarkers for MS. The presenters deemed non-validated experimental markers valuable to study disease biology, but discourage from using them in the clinical practice. Hopefully, new markers with clinical applicability will be discovered over the next few years.

WORKSHOP C – NEUROPROTECTION: WHAT IS IN THE PIPELINE?

ROLAND MARTIN
Zürich, Switzerland

CAROLINE POT
Lausanne, Switzerland

Neuroprotection and regeneration still constitute an unmet medical need in patients with MS.

During the first part of this workshop, Dr Pot explained the different mechanisms that lead to neurodegeneration in MS. She started by reminding the audience that it was previously believed that early in the course of the disease, in particular in the relapsing-remitting form of MS, inflammation and demyelination occurred first, which then subsided giving way to permanent nerve cell degradation in more advanced stages. Scientists know now that axonal damage and neurodegeneration already happen in the early phases of the disease, even before the onset of symptoms.

Several mechanisms participate in the degradation of nerve cells in patients with MS. Whether driven by immune cells (T lymphocytes or innate immune cells), by the production of oxidative species or by depletion of the cells' energy, degenerative pathways cause axon damage, demyelination and programmed cell death.

Until now, most MS treatments attempted to prevent the degenerative processes of the disease to take place. Currently, a new idea has emerged: encouraging regenerative processes and remyelination.

During the early stages of MS, remyelination is driven by oligodendrocytes – cells of the CNS capable of regenerating the myelin sheath of up to 50 different nerve cells. Protecting oligodendrocytes from damage or enhancing their activity are new strategies that are being researched at the moment. The most advanced new therapy of this sort is an anti-lingo-1 antibody: LINGO-1 is a signalling protein that inhibits the maturation of oligodendrocytes and represses remyelination. By binding the active domain of LINGO-1 by an antibody (the anti-lingo-1 antibody), scientists have shown evidence of remyelination and regeneration of nerve cells in mice. More information on the efficacy and safety of this exciting treatment option in patients with MS should be released this year!

Dr Martin proceeded to presenting other therapies that have shown promise as neuroprotective agents. He began by recounting that drug development is a risky and non-rewarding enterprise, and that many regulatory hurdles must be overcome. In addition, the seemingly endless heterogeneity of the patient population adds to the challenges that surround clinical research, making it complicated (and expensive) to obtain data of sufficient quality to warrant the safety and efficacy of new therapies.

One way to overthrow numerous hurdles to drug development is repurposing drugs that are already available. According to Dr Martin, among molecules available for other indications, interesting candidates with potential neuroprotective/regenerative activity in MS are erythropoietin (used mainly to foster red blood cell production, but has many other effects), sex hormones (testosterone and estriol, a pregnancy-related sex hormone), minocycline (antibiotic mostly used to treat acne), and PDE-IV inhibitors (molecules investigated to treat depression, anxiety, and other disorders of the CNS). Dr Martin concluded that further investigation financed by third party sources – such as the Swiss MS Society – is crucial for assessing the potential of these molecules in MS.

WORKSHOP D – BRAIN ATROPHY IN CLINICAL PRACTICE: USEFUL OR NONSENSE?

CRISTINA GRANZIERA
Lausanne, Switzerland

SVEN SCHIPPLING
Zürich, Switzerland

The objective of the workshop was to discuss the question whether measurements of brain atrophy by structural MRI are ready to be used in clinical practice to assess and predict neurodegeneration in MS patients.

MRI offers the best studied and commonly available method to assess the extent of brain lesion, be it inflammatory focal lesions (i.e. spatially confined tissue destruction), or more global brain atrophy. During the course of MS, significant atrophy can develop in the white matter compartment, which comprises mostly glial cells and myelinated axons, and in areas of deep and cortical grey matter in the cortex (the outer layer of the brain), in which the neuronal cells are predominantly located.

In addition to focal lesions that can be detected by conventional MRI-sequences, white matter that appears completely normal (normal appearing white matter (NAWM)) may indeed harbour diffuse tissue damage (diffusely abnormal white matter). To quantify this diffuse damage, measurements of volume changes ("atrophy") appear to be most suitable.

It is known that brain atrophy beyond the level of physiological ageing effects starts early in the disease, even before the first symptoms appear, and that it persists throughout the course of the disease. Data from clinical trials suggest that occurrence is clinically relevant already early in the disease. When researchers looked at early atrophy from patient groups several years later, groups with high amounts of early atrophy had progressed significantly faster to severe MS stages than those patient cohorts with less atrophy. Similarly, early high inflammation load is associated with increased risk of progression.

Generally, brain tissue degeneration matters for patient-related outcomes. Models from patient groups assessing the number and size of inflammatory lesions combined with central atrophy are able of predicting the future disease course on a group level. High and early degeneration and inflammation loads led to a significantly higher risk of converting to clinically definite MS than lower loads. Whether these metrics are predictive of disease progression in individual patients remains to be confirmed.

Crucial for the MRI-based atrophy measurements in individual patients is the question whether or not the assessed changes are indicative of "true" tissue loss beyond endogenous noise of the methodology and therefore meaningful in clinical practice. Repeated measurements with the currently available technologies still reveal a considerable amount of variability, but assessment of brain volume becomes more and more reliable and there is hope that atrophy may be reliably assessed in the near future. Carefully assessing reliability and consistence of imaging protocols and scanners, however, are mandatory to assess brain atrophy on short timescales

Current research focuses on developing protocols that produce atrophy measurements comparable to standardised blood tests. This will allow to quantify brain structure and volume changes and compare them to reliable thresholds of clinically meaningful atrophy. Following repeated scans, it would be clear if the observed volume change is a natural sign of ageing or if the brain volume loss is indicative of neurodegenerative changes observed in more severe disease phenotypes in MS.

ABBREVIATIONS

CNS – Central nervous system

CIS – Clinically isolated syndrome

CSF – Cerebrospinal fluid

DMTs – Disease modifying therapies

EBV – Epstein-Barr virus

HLA – Human leukocyte antigen

JCV – John Cunningham virus

MRI – Magnetic resonance imaging

MS – Multiple sclerosis

NMO – Neuromyelitis optica

PCR – Polymerase chain reaction

PML – Progressive multifocal leukoencephalopathy

RRMS – Relapsing remitting MS

SMSC – Swiss MS Cohort

SMSR – Swiss MS Registry

Colophon

This meeting report was produced by Medicalwriters.com LLC and commisioned by the Swiss MS Society. The content of this report is based on the presentations given during the 18th State of the Art Symposium in Luzern, Switzerland on 30 January 2016.

Agency

Medicalwriters.com
Limmatstrasse 107
8005 Zürich
Switzerland
Telephone: +41 43 508 03 13
Email: info@medicalwriters.com
Web: www.medicalwriters.com

Kindly supported by


AUFGEBEN IST KEINE OPTION.
HELFEN SIE MS-BETROFFENEN DURCHZUHALTEN.
PK 80-8274-9 www.multiplesklerose.ch
MS
Schweizerische Multiple Sklerose Gesellschaft