NASA Neurological Association of South Africa

CONFERENCE HIGHLIGHTS: ECTRIMS 2019

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"Picture taken from ECTRIMS talk 2019"

I was privileged to be part of a group sponsored to attend ECTRIMS after almost a decade. Stockholm was the host city for 2019 and it was co-incidentally my second visit to Stockholm. Unlike my eternal romance with most European cities, I find Stockholm to be rather confusing – it's renowned for technological innovation but looks like a strange wooden town painted in muted shades of yellow and blue; lacking the majestic castles and cathedrals so typical of Europe.

The conference boasted 10 000 delegates and was a real gourmet feast of information. I must confess there were moments of complete saturation and one was ultimately glad when it was tea time.

My personal favourites were the debate sessions – I attended one on the interferons and another on stem cell treatment. The take home message was HSCT has a quicker time to NEDA (no evidence of disease activity) than

disease modifying agents, and a sustained benefit, in RRMS, but not in progressive MS. Counter-intuitively, the latter is where we generally tend to look for bigger guns and justify greater risks.

The NMO sessions were a bonus – it is encouraging to hear that there are 3 new treatments available – more specific and directed against the aquaporin antibodies rather than the broad spectrum immunosuppressants we currently use.

As science progresses and imaging yields almost biological information, one gets the impression that the classification of MS is dated and artificial. MS is a progressive disease from the start – PIRA is a term referring to "progression in relapse absence". Hence there probably will be a time when we will shift to referencing an "inflammatory" phase and a "degenerative" phase. The standard first line treatments seem increasingly redundant: they're recommended for milder disease. But we all know trying to enforce regular injections in a well patient with only a wonky leg isn't a happy experience.

Which makes the new kids on the (South African) block a welcome addition. Both agents are given in short courses, have long-lasting effects allowing patients a greater measure of "normal" life between doses (provided they don't have side effects, of course). Cladribine, (Mavenclad) is an oral agent administered for 2 weeks per year, for 2 years. It is currently recommended for highly active relapsing MS and is still awaiting MCC release in South Africa. But it has been in use in Australia for 9 years and appears very well placed. Use of Cladribine Tablets in MS is supported by over 14 years of clinical trial experience. For both talks the point was made that early, high-efficacy therapy may slow progression and improve long-term outcomes.

Ocreluzimab, (Ocrevus) is a monoclonal antibody that binds to a molecule (CD20) on the surface of B cells, and reduces the numbers of certain B cells that are circulating. Ocrelizumab is administered by intravenous infusion every 6 months. The first dose is given in two infusions, two weeks apart. Subsequent doses are given as a single infusion.The U.S. Food and Drug Administration has approved Ocrevus™ for use in the treatment of primary progressive MS and relapsing MS, making it the first therapy for the treatment of primary progressive multiple sclerosis.

Another major theme was the resurgence of use of real-world evidence mainly in the form of Registries for continued surveillance and identification of gaps in clinical research.

Family planning remains paramount and topical. Although many Registries are providing safety information, Copaxone is licensed as safe in pregnancy.

Serum NFL levels are gaining ground as a biomarker.

Dr Marcell Britz was part of our group and cites the epigenetics session as his favourite learning. His summary follows:

Epigenetics in MS: Implications for pathogenesis and disease management.

Epigenetics a relatively new field in medicine. Epigenetics, as a simplified definition, is the study of biological mechanisms that will switch genes on and off – and basically determines how cells (the individual?) interacts with the environment.

Evolutionary pressure has led cells to develop mechanisms that are able to sense and respond to an ever-changing environment by adjusting their gene expression. The epigenetic cellular machinery is vital for this cross-talk between cells and the environment and its dysregulation has been implicated in several autoimmune diseases, including multiple sclerosis (MS).

At least three systems including DNA methylation, histone modification and non-coding RNA (ncRNA)-associated gene silencing are currently considered to initiate and sustain epigenetic change

Epigenetics affects how genes are read by cells, and subsequently whether the cells *should* produce relevant proteins or not. Each cell nucleus at any given moment is switched on (engaged) in a unique status – engaging only specific genes to be read with the greater majority of genes switched off. This allows for epigenetic fingerprinting – making it possible to detect deferentially methylated circulating-free DNA in serum of patients with active MS disease.

The hypothesis then that neuronal injury will result in debris escaping through the BBB into the circulation – and by measuring demethylation patterns of the myelin oligodendrocyte glycoprotein (MOG) gene in O4+ ODCs in mice and in DNA from human oligodendrocyte precursor cells (OPCs) – it was possible to utilize this potential biomarker to – in real time – measure oligodendrocyte injury. This technique promises to allow for a minimally invasive procedure to monitor disease activity in patients with active or stable MS.

The transcription factor cAMP-responsive element binding protein (CREB) is a multifaceted regulator of neuronal plasticity and protection.

Research has shown levels of CREB to be reduced in NAWM (normal appearing white matter) in patients with MS.

CREB is a critical component of the neuroprotective transcriptional network, and data indicating that CREB dysregulation contributes to an array of neuropathological conditions – and further research has shown that CREB activity can be modulated through epigenetic mechanisms – and both Fingolimod and Biotin has a direct epigenetic effect on CREB levels in the CNS.

In the third presentation the investigator considered the possibility of accelerated ageing in patients with MS – as has been documented in patients with PD.

The – Epigenetic clock (DNA methylation age) is in essence the specificity by which the methylation status of some cytosine-guanine dinucleotides changes with age. Although changes to DNA methylation state are known to occur with age, it is nevertheless a surprise to behold the remarkable precision of this change and that it can lend itself as a measuring stick of biological age. The study failed to show any evidence of accelerated aging in patients with active / non-active MS.

Summary:

Even though the hope of modifying epigenetic switches to alter the outcome of MS pathogenesis in a significant way remains elusive, the real possibility of utilizing epigenetic techniques to monitor MS disease activity seems far more likely to be implemented in the not too distant future.