Module 4: Small clues, big changes – Biology-guided treatment decisions in MS

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Introduction

Dr Marcello Moccia:

Welcome to Module 4: Small clues, big changes – Biology-guided treatment decisions in MS

There is increasing emphasis on integrating clinical observations with biological and imaging markers to guide treatment decisions. Subtle changes, when recognised early, can provide critical insights into disease activity and progression.

Dr Ahmed Abdelhak joins us in this final module to explore how these signals can be interpreted in clinical practice and how they can support more precise, individualised care.

Understanding Progression in MS

Dr Ahmed Abdelhak:

I'm Dr Ahmed Abdelhak. I'm an Assistant Professor at the University of California, San Francisco. I'm a neurologist and neuroimmunologist, and today I'm going to talk to you about some small clues that we have in our care arsenal, or in our MS care management tools, that can help us derive biology-guided treatment decisions, particularly focusing on progression in multiple sclerosis.

The most challenging aspect of treating multiple sclerosis at present is diagnosing, treating and potentially preventing disease progression, which, as many of you know, is an irreversible process. Early detection is therefore key for proper management of our MS cases.

The challenging part is that there is not only one type of progression. We currently recognise at least two types of progression in the clinical setting: relapse-associated worsening, sometimes referred to as RAW, and progression independent of relapse activity, or PIRA.

Relapse-Associated Worsening and PIRA

Relapse-associated worsening is straightforward from its name. These are patients who develop relapses, and those relapses lead to an increase in their EDSS. The most common definition is within 90 days, although other timelines may vary.

This is different from classical relapses, which are usually associated with complete reversal of symptoms within a few weeks. Here, we are talking about patients who experience irreversible damage from relapses.

The other type, progression independent of relapse activity, has nothing to do with clinically manifested activity. There is even further classification of progression independent of relapse and MRI activity, which means the patient does not have relapses, and if MRI is performed, there are no changes in the context of new lesions or gadolinium-enhancing lesions.

Each of these types of progression requires a different approach to early detection and has different therapeutic consequences related to the mechanisms driving progression.

Clinical and Biological Risk Signals

For relapse-associated worsening, the key issue is disease activity. The factors that help us predict and manage this type of worsening are similar to those used in the context of MS activity.

These include younger patients, patients with highly active disease, patients who have had many relapses in the past, or patients with many signs of activity on MRI.

Blood biomarkers may also help. For example, elevated neurofilament light chain may indicate a higher risk of disease activity and therefore relapse-associated worsening.

For patients who fulfil this risk profile, it is important to consider treatments that are highly effective in suppressing disease activity, while also taking into account the overall patient profile, comorbidities and patient preferences.

Here, we are talking about patients with high activity who may benefit from highly effective disease-modifying treatments that can almost completely suppress detectable disease activity.

Why PIRA Remains Challenging

When we think about PIRA, or progression independent of relapse activity, it becomes much more challenging for two reasons.

First, we do not fully understand what drives it.

Second, at least so far, we do not have approved treatments that specifically target these components of the disease.

We know that glial cells, for example, may drive at least some of the events we call PIRA in the context of compartmentalised inflammation within the brain.

In these cases, we may not see a severe systemic immune response or lymphocyte recruitment from the blood into the brain. Instead, we may see microglia or astrocytes activated within the brain, contributing to neuroaxonal injury.

Biomarkers and Emerging Treatment Strategies

In some of the research we have conducted, we observed elevated neurofilament light chain and elevated GFAP, a marker of astrocytes, preceding the diagnosis of PIRA.

This suggests that damage occurs in the brain over a prolonged period before we even diagnose these events clinically.

We also know that even our highly effective treatments currently play only a minor role in controlling this inflammation within the brain.

Some newer emerging treatments, potentially including BTK inhibitors, may contribute to managing these events. Some data have shown substantial reductions in confirmed disability progression in both relapsing and purely progressive forms of multiple sclerosis. This may

suggest a preferential effect within the CNS, contributing to reduced compartmentalised inflammation, particularly involving microglia.

However, this is still an emerging field. We need to better understand what drives these events, how to prevent them, and hopefully, in the future, identify treatments that can influence them.

Closing Statement

Dr Marcello Moccia:

Thank you, Dr Abdelhak. That was an excellent presentation.

I believe that the use of biomarkers combined with clinical features in clinical practice can help guide treatment decisions and ultimately improve the prognosis of people living with multiple sclerosis.

Detecting and acting on signs of progression is central to improving outcomes in multiple sclerosis.

By combining clinical insights with evolving tools and technologies, we can move towards more proactive and personalised care.

Thank you for joining this series.