A NEW ERA IN MULTIPLE SCLEROSIS

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Ipsos

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Introduction

In our 2019 point of view (PoV), **Shifting Paradigms: High-efficacy Therapies in MS Treatment**, we discussed the growing use of 'high-efficacy' disease modifying therapies (DMTs) earlier in the multiple sclerosis (MS) treatment pathway, any nuances in the patient types being treated with these therapy options, and any recorded benefits of doing so.

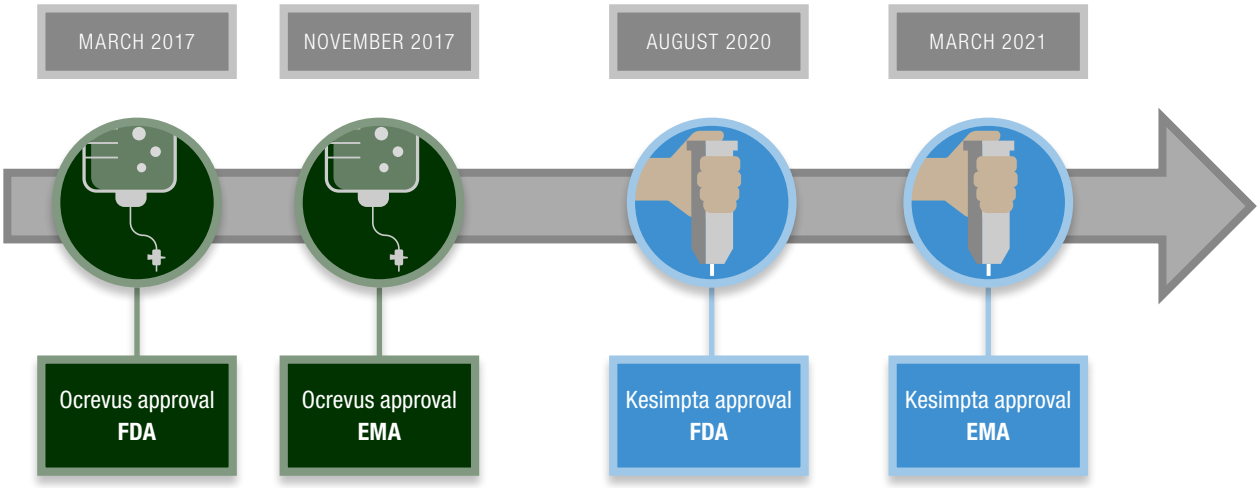
Three years on, we revisit the stage to assess any further impact seen on the MS treatment algorithm now that two anti-CD20 products are available. Using Q4 2019 and Q4 2021 data from Ipsos' syndicated Multiple Sclerosis (MS) Therapy Monitor in the EU4 + UK and the US, we will present the ongoing evolution of treatment dynamics seen in reported MS patients and their treatment pathway, and how neurologists* perceive the anti-CD20s versus more traditional therapies. We also offer a look to the future, hypothesising about any effects on MS progression rates and the potential of the MS treatment pipeline.

**While we refer to 'neurologists' throughout the article, our sample physician set also includes specialised MS nurses in the UK dataset.*

The anti-CD20s

Whilst the group of 'high-efficacy' DMTs in MS can be considered as consisting of the brands Gilenya, Tysabri, Lemtrada, Mavenclad, Mayzent, Ocrevus, Kesimpta, and recent oral launches, Zeposia & Ponvory, for the purposes of this article we focus specifically on available agents that centre on the contribution of B cells in the pathogenesis of MS – the anti-CD20 therapy class. Ocrevus was the first anti-CD20 to market, receiving FDA approval in March 2017 to treat relapsing forms of multiple sclerosis (MS) and primary progressive multiple sclerosis (PPMS) – it was noteworthy as it was the first drug approved by the FDA for PPMS[1]. Its EMA marketing authorisation was then granted in November 2017[2]. Kesimpta followed three years later, receiving FDA approval in August 2020 to treat relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease[3]. Its EMA approval for patients with relapsing forms of MS with active disease followed in March 2021[4]. A key difference for Kesimpta was its self-administration. [FIGURE 1]

Figure 1: Anti-CD-20 approval timeline in MS

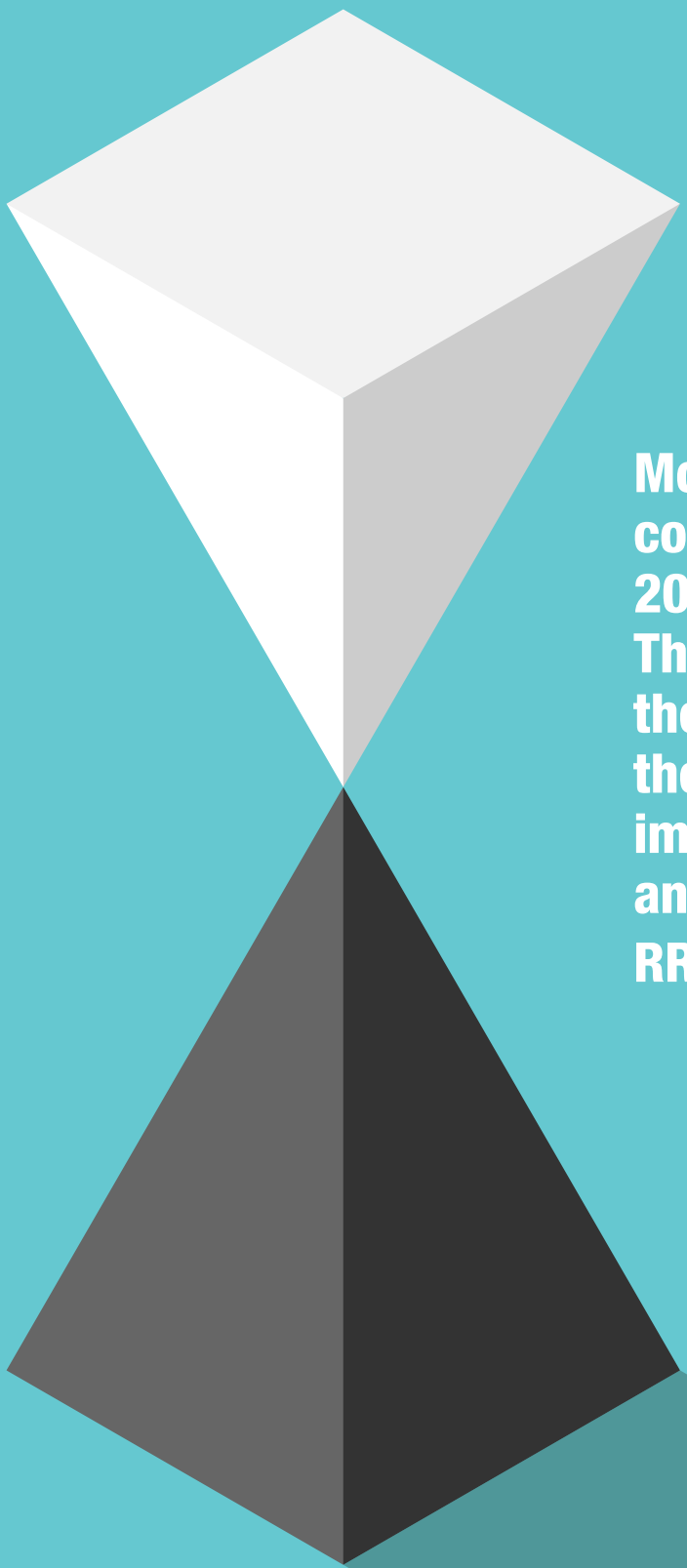


Have the anti CD20s made a difference to the treatment pathway for MS patients?

In our 2019 PoV, we highlighted an increase in the proportion of reported 1st line relapsing remitting (RRMS) patients who had initiated onto a high-efficacy option between Q4 2015 and Q4 2018 (14% vs 27%, EU4 + UK; 17% vs 33%, US)[5**]. This data had already suggested a shift in sampled neurologists' mindsets in terms of comfort in using more aggressive treatments earlier in the treatment pathway, versus the more traditional 'platform therapies' (interferons, glatiramer acetate, teriflunomide and fumarate options, collectively).

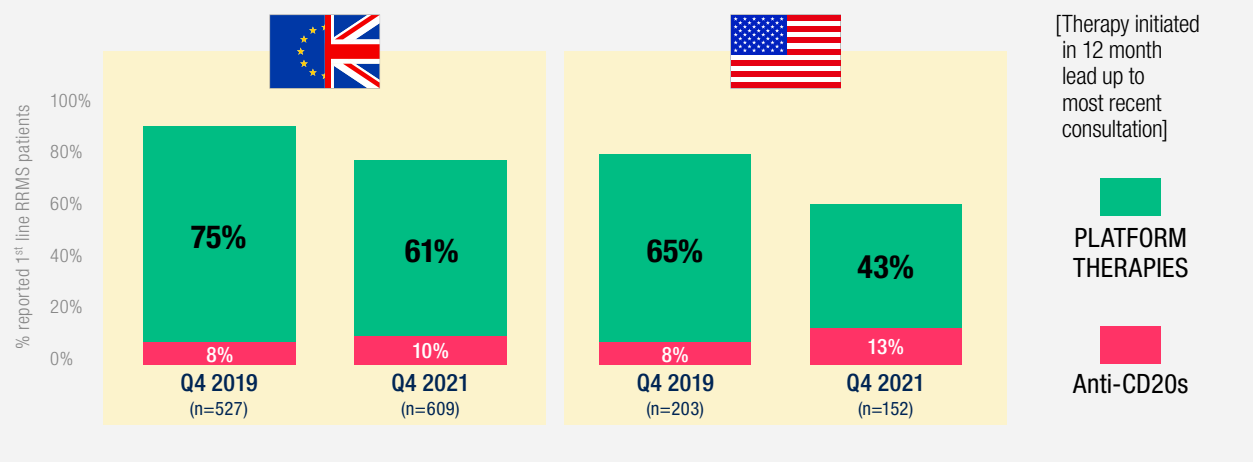
Moving forward to compare Q4 2019 and Q4 2021 data from our MS Therapy Monitor, we note the anti-CD20s come into the fray and show specific impact across both 1st and 2nd line reported RRMS patients: amongst the 1st line patients who started therapy in that same year, 8% in Q4 2019 were recorded as receiving an anti-CD20 vs 10% in Q4 2021 in the EU4 + UK data; a slightly greater shift is seen in reported US data, depicting an anti-CD20 share of 8% in Q4 2019 vs 13% in Q4 2021.

Admittedly, this increase is likely to be influenced partly by anti-CD20 brand availability and time on market but decreases in platform therapy usage over these same timeframes suggests a continued move towards more targeted, newer, high-efficacy treatments versus more traditional options. [FIGURE 2]



Moving forward to compare Q4 2019 and Q4 2021 data from our MS Therapy Monitor, we note the anti-CD20s come into the fray and show specific impact across both 1st and 2nd line reported RRMS patients

Figure 2: Reported 1st line RRMS patient market share of anti-CD20s vs platform therapies

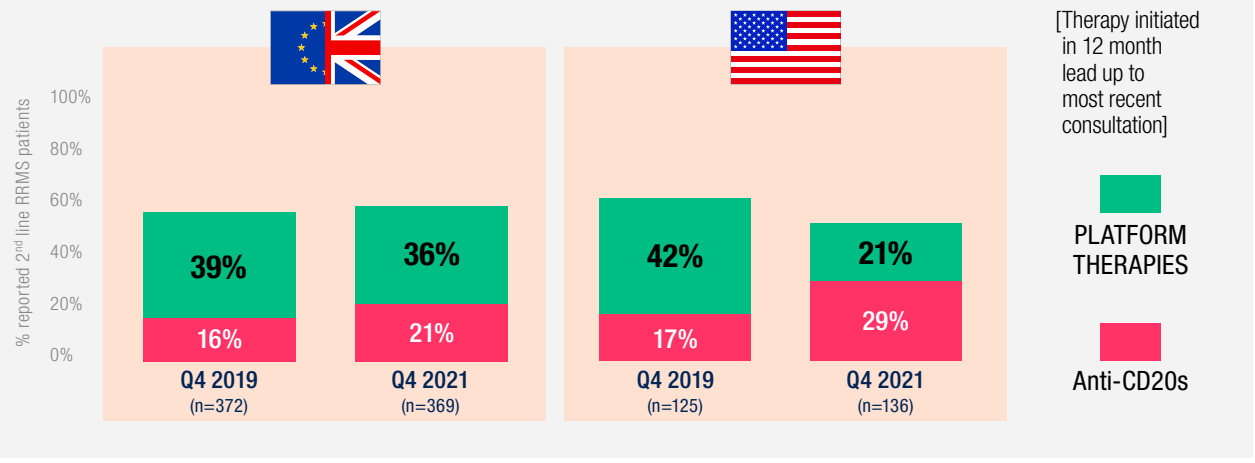


SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2019, 309 neurologists / MS nurses in EU4 + UK (equal split across countries) and100 neurologists in US; Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) and 116 neurologists in US reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

Platform therapies = interferons, glatiramer acetate, teriflunomide, fumarate options
Anti-CD20s = Ocrevus, Kesimpta

This is further corroborated by our data on reported 2nd line RRMS patients who started therapy in the same year: anti-CD20 share increases between Q4 2109 and Q4 2021, as platform therapy share decreases. [FIGURE 3]

Figure 3: Reported 2nd line RRMS patient market share of anti-CD20s vs platform therapies



SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2019, 309 neurologists / MS nurses in EU4 + UK (equal split across countries) and100 neurologists in US; Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) and 116 neurologists in US reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

Platform therapies = interferons, glatiramer acetate, teriflunomide, fumarate options
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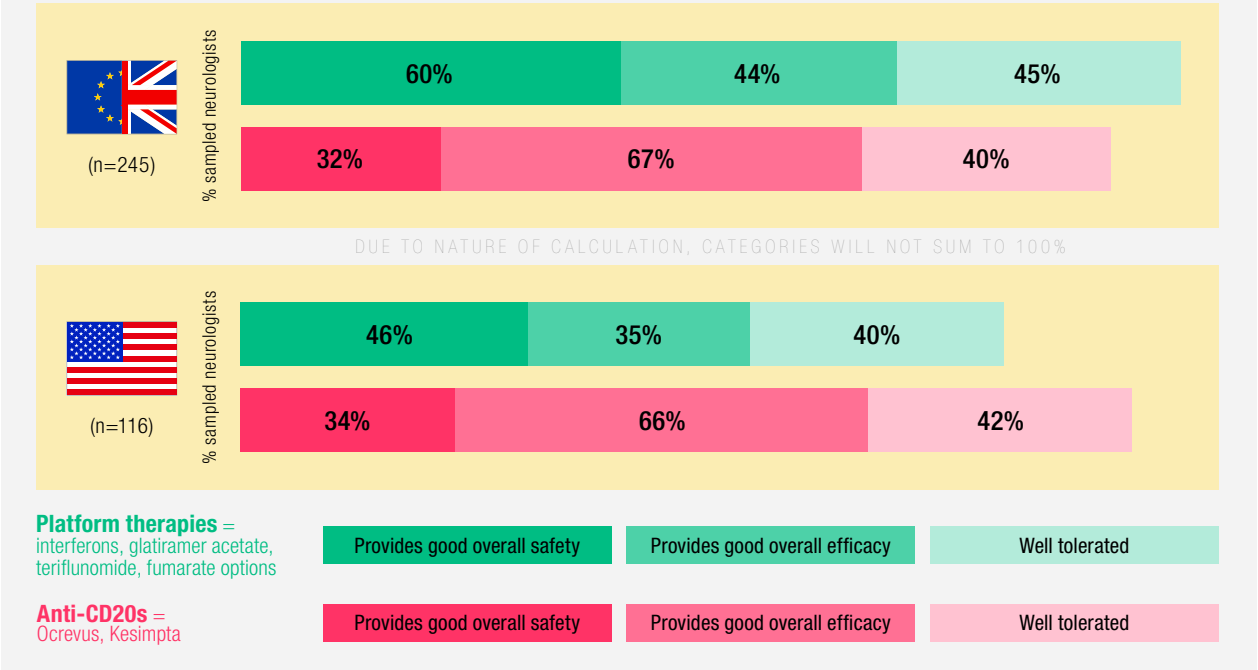
This data not only speaks to ongoing comfort in using high-efficacy DMTs earlier in the treatment pathway, and further adopting a 'treat early, treat aggressively' approach, but it speaks to comfort in specifically using this newer, targeted therapy class upfront.

How are neurologists' perceptions changing towards the anti-CD20s?

If there is indeed an ongoing tendency to use high-efficacy DMTs ahead of the traditional platform therapies, what is driving neurologists' decision to do so?

Whilst efficacy as an overall driver of MS therapy usage has been seen to decline over time in favour of more nuanced attributes, it remains the primary reason for therapy choice in our reported patients initiating MS therapy (notably, our data shows greater decline as a primary driver for platform therapies versus. high-efficacy DMTs). When viewing sampled neurologists' overall efficacy, safety & tolerability perceptions of the anti-CD20s versus platform therapies in Q4 2021 across both EU4 + UK and US datasets, collectively the anti-CD20s are perceived as more efficacious to the platforms, and have similarly perceived tolerability levels; safety perceptions, on the other hand, favour the platform therapies. [FIGURE 4]

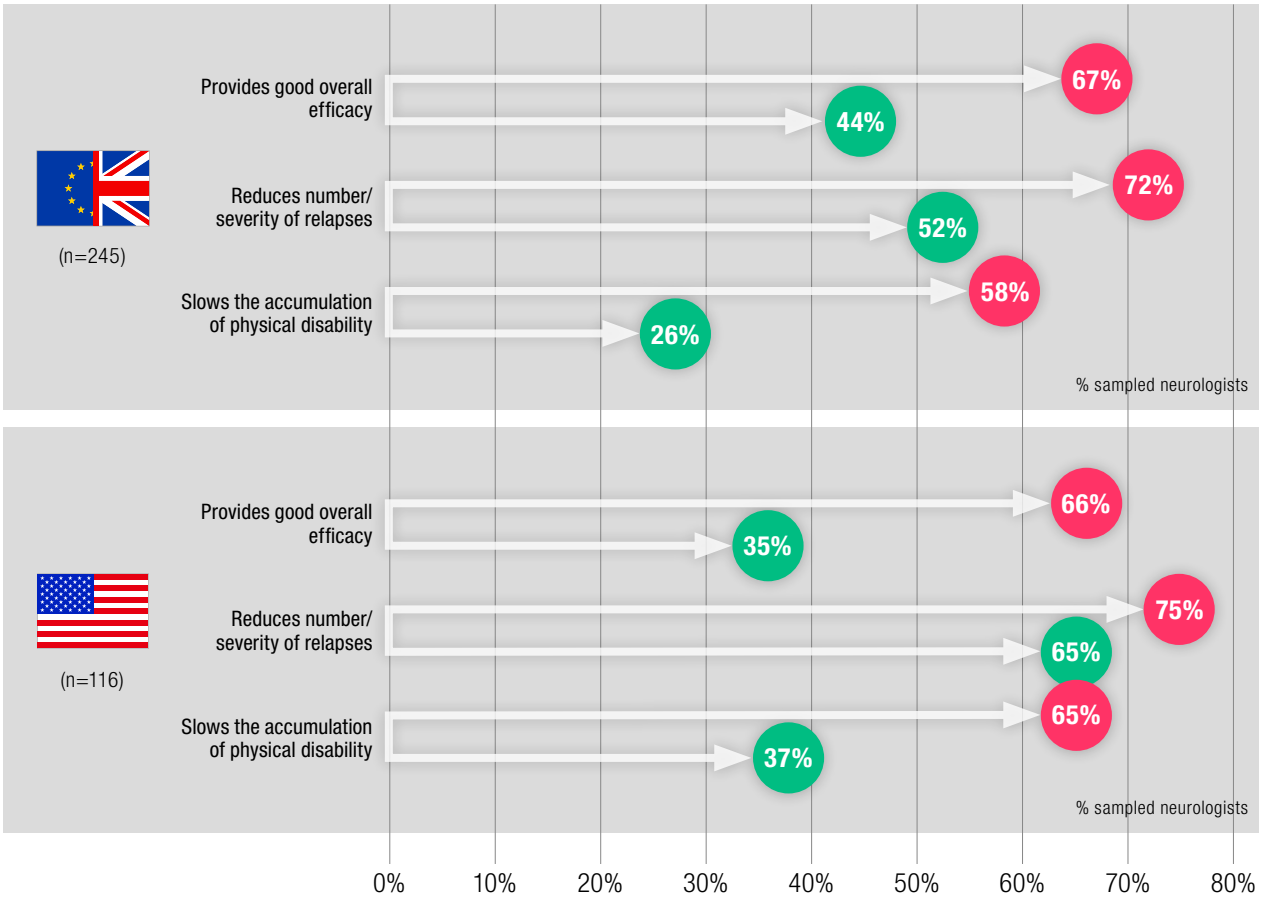
Figure 4: % of sampled neurologists associating anti-CD20s vs platform therapies with overall efficacy, safety & tolerability (Q4 2021)



SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) and 116 neurologists in US reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

Specifically, the attributes '*provides good overall efficacy*', '*reduces number / severity of relapses*', and '*slows the accumulation of physical disability*' are considered the top three most important drivers for choosing a DMT therapy by our participating neurologists in both the EU4 + UK and US, and are three attributes with which they more highly associate the anti-CD20 therapy class versus platform therapies; '*substantially improves patient quality of life*' is an additional key driver that anti-CD20s are more highly associated with versus platform therapies, which highlights a more holistic therapy perception that is not necessarily solely efficacy-focused. Neurologists' associations with specific features such as these may help explain why CD20s are carving out successful in-roads in the MS treatment pathway. [FIGURE 5]

Figure 5: % of sampled neurologists associating anti-CD20s vs platform therapies with top perceived efficacy attributes (Q4 2021)



Anti-CD20s = Ocrevus, Kesimpta

Platform therapies = interferons, glatiramer acetate, teriflunomide, fumarate options

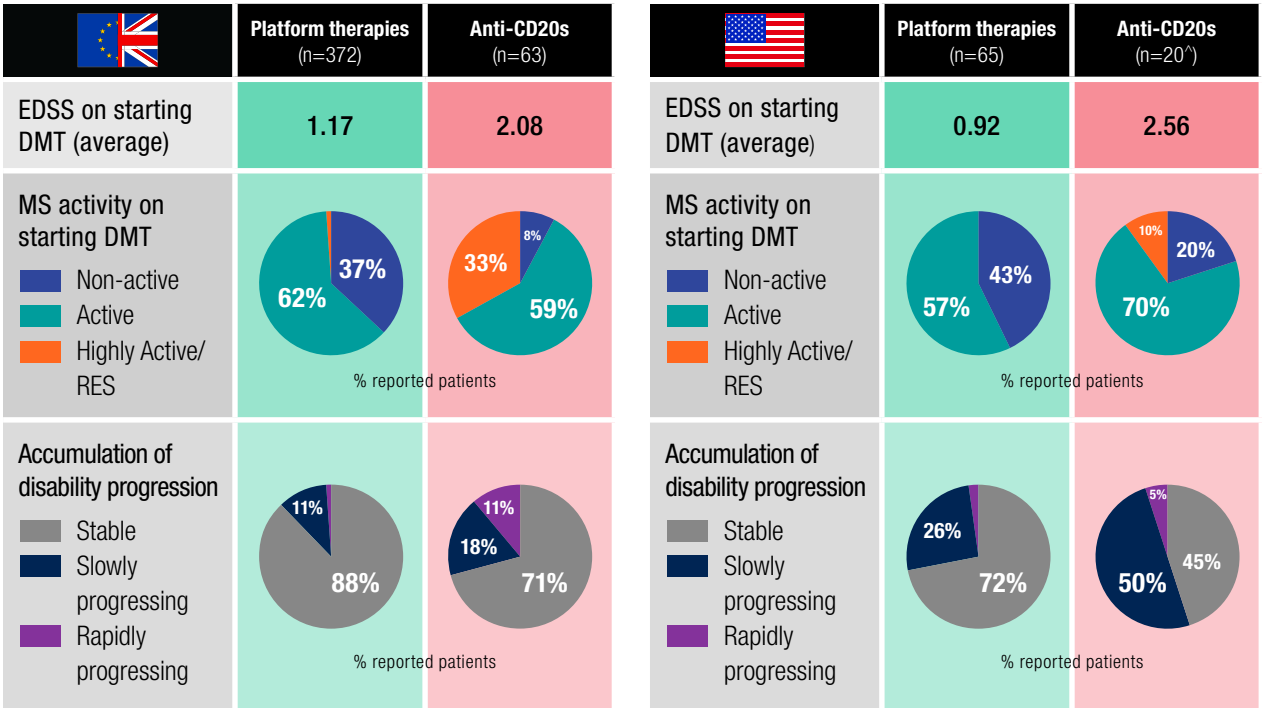
SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) and 116 neurologists in US reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

Are the patient types who receive high-efficacy options changing?

Going back to our 2019 PoV, whilst we saw an earlier adoption of high-efficacy DMTs in our 2015 versus 2018 data, we also observed them being reserved for those with more active disease, pertaining to a better DMT 'match' to a patient's disease profile. On the flip side, we also reported a cohort of active 1st line RRMS patients still being prescribed more traditional DMTs, suggesting a remaining divide in the neurologist community of how best to treat new-to-therapy RRMS patients[5].

Stepping forward to Q4 2021, we note similarities in the usage of anti-CD20s in patient cohorts exhibiting a more active MS disease state: across both our EU4 + UK and US datasets, greater proportions of reported patients who initiated a 1st line anti-CD20 within 12 months of their latest physician consultation had a higher Expanded Disability Status Scale (EDSS) score and were more likely to be recorded as highly active / rapidly evolving severe (RES) when starting their DMT, compared to those initiating a platform therapy. In addition, a greater proportion of the anti-CD20 cohort were considered 'rapidly progressing' in their disability progression. [FIGURE 6]

Figure 6: Reported 1st line RRMS patient profiles of those receiving anti-CD20s vs platform therapies (Q4 2021)



Platform therapies = interferons, glatiramer acetate, teriflunomide, fumarate options Anti-CD20s = Ocrevus, Kesimpta

^denotes base <30; use indicatively

SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) and 116 neurologists in US reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

Whilst high-efficacy agents are being used as an upfront therapy, the data highlights the ongoing clinician mentality to use them in a more nuanced, prescriptive way in patients exhibiting a higher disease burden

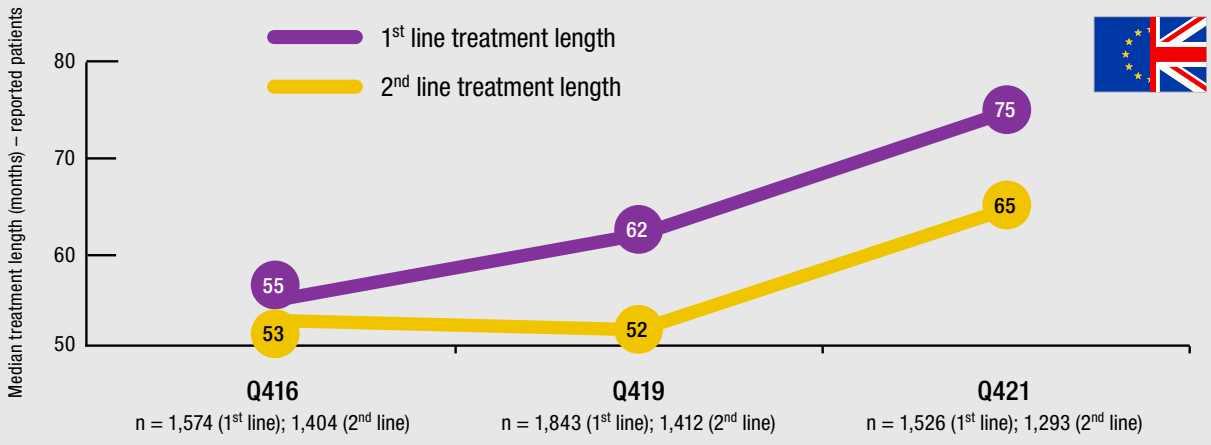
Whilst these high-efficacy agents are being used as an upfront therapy, this data highlights the ongoing clinician mentality to use them in a more nuanced, prescriptive way in patients exhibiting a higher disease burden. It must be noted that the European label does stipulate usage in active patients, so this will influence the above findings, but we believe there are two notes of interest to point out: 1) a proportion of CD-20 usage remains attributed to 'highly active' patients, suggesting there remains a cohort of prescribers still reserving high-efficacy treatment for higher disease burden, and 2) notable proportions of platform therapy usage across both regions relates to 'active' patients, suggesting there still remains disparities among the treating community of how best to treat this patient type. In summary, the sands have not fully shifted yet.

Is 'treat early, treat aggressively' having an impact on progression rates?

In a February 2022 post on his MS Selfie newsletter site, Professor of Neurology, Gavin Giovannoni, discusses the positive implications for disease outcomes and survival in MS patients treated early, and champions the usage of high-efficacy treatments earlier in the treatment paradigm to achieve a more favourable prognosis, i.e., 'flipping the pyramid'[6].

We are yet to see in our datasets if treating earlier with more 'aggressive' therapeutic approaches results in a delay in progression of reported patients' MS disease – it is possible that it is still too early to tell in our methodology, and further monitoring is required. What we do note, however, in our EU4 + UK data is an increase in median time spent on both 1st and 2nd line DMT therapy since 2016. [FIGURE 7]

Figure 7: Kaplan Meier analysis - median treatment lengths of reported RRMS patients who have ever received a DMT at 1st / 2nd line



SOURCE: Ipsos Multiple Sclerosis (MS) Therapy Monitor (Oct – Dec 2016, 275 neurologists / MS nurses in EU4 + UK (equal split across countries); Oct – Dec 2019, 309 neurologists / MS nurses in EU4 + UK (equal split across countries); Oct – Dec 2021, 312 neurologists / MS nurses in EU4 + UK (equal split across countries) reporting on a quota of RRMS, PPMS & SPMS patients. Participating physicians were primary treaters, spent a minimum amount of time in clinical practice and saw a minimum number of MS patients each month (UK, FR, IT, ES, US), or each quarter (DE)). Data collected online. Data © Ipsos 2022, all rights reserved.

At this stage, we could hypothesise that an increase in time spent on a particular DMT may imply a delay transitioning to a more progressive state of MS – again, further monitoring of our datasets is required, and we caveat that this duration trend is not mirrored in our US data.

Looking to the future

Future potential expansion of the MS treatment landscape includes a third anti-CD20, ublituximab[7], and a class of therapies called Bruton's tyrosine kinase (BTK) inhibitors. Four of these are currently in phase 2 and 3 trials and, based on their immunomodulatory properties, offer additional targeted specificity potential for treating relapsing and progressive MS[8].

We have seen in the Ipsos datasets an ongoing drive among the MS-treating sample to adopt the use of high-efficacy DMTs earlier in the MS treatment pathway, including new players that become available. Their nuanced use in more active patients, and their apparent influence on what is important when considering why to use them, suggests ongoing willingness to start patients with stronger therapies to limit disease progression and ultimately improve patient outcomes.

With this openness and the pipeline potential, we strive for a future where the pyramid truly is flipped.

About the Research

The Ipsos Multiple Sclerosis Therapy Monitor is a physician / MS nurse-reported syndicated patient record database, capturing prescribing of treatment for MS patients. Participating physicians / MS nurses are screened for specialty, time spent in clinical practice, number of MS patients seen each month (UK, FR, IT, ES, US) or each quarter (DE) and must be the primary decision-maker for their patients. Each wave, participants provide demographic information, de-identified information on a quota of 6 to 15 RRMS, PPMS & SPMS patients seen in consultation, and responses to a perceptual questionnaire. Data used in this article were collected online. Sample sizes are provided alongside the relevant charts.

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