Progressive multiple sclerosis treatment considerations in the UK: experience from trials and real-world population

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Abstract

The recent availability of disease modifying treatments (DMTs) for progressive multiple sclerosis (PMS) is a welcome change, yet the limitations of clinical trial design and the real-world makeup of the PMS population necessitate a balanced view of their potential benefits and risks in a population that is on average older than the relapsing-remitting MS (RRMS) population, and more likely to have or develop comorbidities over time. Here we will review the available data for DMT efficacy and risks in PMS with a view to guiding clinician and patient in joint care decision making.

Introduction

People with RRMS (pwRRMS) comprise the majority of new MS diagnoses, however a significant proportion of pwRRMS go on to develop secondary progressive (SPMS). Early natural history studies suggested this to be as high as 90% of pwRRMS by 25 years, at a conversion rate of approximately 2-3% per year [1,2], though recent studies suggest this might be lower (35-62% by 20 years, up to 75% by 30 years) due to DMT use [3-7] and predicated on other risk factors [8-10]. In addition, 10-15% of new diagnoses consist of primary progressive MS (PPMS) [11]. Considering that the total number of people with MS (pwMS) in the United Kingdom (UK) is approximately 130,000 [12], this means that there are at least 50,000 people with PMS at any one time point [13]. Lastly, with the advent of multiple high efficacy therapies, it's appreciated that MS exists on a spectrum, with progression occurring independently of relapses, and during the RRMS phase [14-16].

The licensed treatment option in the UK for active PPMS is ocrelizumab [17], and for active SPMS include either siponimod [18] or rarely, Interferon beta-1b (brand name Extavia) [18]. Their initiation requires evidence of MRI or clinical relapse to be eligible. Trial design, however, targets statistical significance for the primary efficacy outcome measure rather than secondary safety analyses, and there is no agreed gold standard definition of a true risk signal from safety monitoring. These issues are compounded by the recruitment of a lower-risk population, inconsistencies in adverse event reporting and misclassification, and lack of generalisability from either the trial population or a restricted dosage regime [19].

This is of salience in PMS which occurs more frequently in an older and more vulnerable population group (mean age of onset is 45 years in SPMS [20], and 40 years in PPMS [21]), as well as the increasing mean life expectancy in MS, from a historic expectancy of 66 years to more recent studies suggesting around 75 years [22-26].

The Importance of Age

Age appears to be a major determinant of DMT effect, a meta-analysis of clinical trial data identified reduced likelihood of efficacy after age 53 in the average pwMS [20]. Compounding this is the potential risk of side effects such as opportunistic infection, malignancy, and autoimmune events, which are more likely with advancing age or greater duration of treatment [27-30].

Immunosenescence is more likely with advancing age, with age-related changes in both adaptive and innate immune cells [31] being seen. This can contribute to the risk of cancer [32], opportunistic infections (including rare cases of progressive multifocal leukoencephalopathy ((PML)), or worse outcomes following infection [22,33-34].

Additional risk arises from other conditions that more commonly develop with age, such as hypertension, diabetes, ocular pathology, and cardiovascular disease. A recent UK-based study simulated evidence that 2/3 of the adult population older than 65 years will be living with multiple comorbidities by 2035 [35].

Beta Interferons (INF-β)

Extavia (interferon β-1b, INF- β-1b) is

Table 1. Impact of interferons on infection risk - from [42]

	Bacterial Infection	Viral Infections	Fungal Infections	Protozoa and parasites
INF- β-1b	● No increased risk of infections ● Local infections at injection site possible	Possible antiviral effect on HBV/ HCV, no risk of reactivation in chronic viral hepatitis	No increased risk of infections	Possible protective effect against Leishmania

licensed for SPMS with relapses by NICE [36], however from internal calculations the overall number of pwSPMS on Extavia is likely to be ≤1%. INF- β-1b has been the subject of extensive experience and longitudinal study and has consistently been found to be a safe medication [37-40].

The infection risk is limited, with a minimal demonstrable increased rate of crude infections compared to the general population (incidence rate, 8.9% vs 5.2% per 1000 person years) [41]. It is not associated with opportunistic infections [42], and the only reported case of PML with interferon monotherapy occurred in an individual with common variable immunodeficiency syndrome [43].

Within one observational study over 12 years [40], a non-significant trend towards risk of breast cancer cases in those treated with INF-β (OR 1.77) was seen – however without a dose-response effect or discrepancies in tumour size. Another, smaller study from Israel of 1,338 pwMS demonstrated a borderline association with non-breast cancer risk that did not reach statistical significance [40].

Larger studies, including a French study involving 12 MS centres, revealed no increased risk of cancer with any IFN-β exposure [44], supported by post-marketing industry-sponsored studies of insurance claims showing no increase in cancer rates – however both were over a brief 2–3-year period only [45-46].

The efficacy of continued interferon use is debatable; an Italian study [47] demonstrated that of an SPMS cohort, divided into two groups, one continuing treatment for a minimum of 36 months, and the other stopping, there was no difference in accrual of an extended disability score (EDSS) of 7.0 over a 10-year period.

Siponimod for SPMS

Siponimod rapidly depletes T lymphocytes from the peripheral circulation by sequestering them within lymphoid tissue, thereby preventing them from migrating to the central nervous system (CNS), and potential further impact on CNS cells [48]. Siponimod acts only on sphingosine-1-phosphate-receptors 1 and 5, reducing the risk of adverse effects [49-50].

The EXPAND trial demonstrated siponimod's efficacy in cases of active SPMS in 2018, with a significant reduction in 3-month confirmed disability progression (CDP) (21% reduced HR), and subgroup analysis demonstrating a marked reduction in both 3-month CDP (36% reduced HR) and 6-month CDP (41% reduced HR) versus placebo [51]. Its side effect profile is well documented and summarised in Table 2.

A German retrospective multi-site observational study [50] of 227 pwSPMS over an 18-month period, supported the benefits of siponimod. At 12 months, almost 65% had experienced disease stability (and improvement in 21.4%).

EXPAND highlighted infection as a significant complication of siponimod vs placebo, specifically for varicella zoster virus (VZV) reactivation (2% vs 1%) and herpes infection (5% vs 3%), including one case of herpes zoster (HZ) meningitis. In the context of age and age-related co-morbidities, 68% of VZV infections in the general population occur after the age of 50 [49,50], with relative risk of infection increasing by 1.65 times after the age of 60. A variety of comorbidities (including diabetes, cardiovascular and renal disease, and rheumatoid arthritis) contribute to this risk further (RR range, 2.08-1.23) [53].

COVID-19 related data has been encouraging, with evidence that siponimod use doesn't predispose to higher risk of severe outcomes [54], however it does impair the humoral vaccine response [55,56].

PML has been reported in 3 cases, one in the EXPAND trial extension, and two in post-marketing. Two have been attributed to siponimod directly, in a 63-year-old male and 62-year-old female, with the duration of use being 6.5 years and 8 years respectively [57].

Though skin cancer rates in the EXPAND study were similar between cases and controls (all skin neoplasms n=14/1099 vs n=8/546, and BCC n=11/1099 vs n=6/546, respectively), it raised concern of potentially increased skin cancer risk [51]. A recent real-world study utilising the FDA adverse event reporting system, showed patients on siponimod were 11.32 times more likely to develop skin cancer (crude reported odds ratio). On further sensitivity analysis, basal cell carcinoma (BCC) was 22.83 times more likely to occur in the treatment group vs placebo [58].

Significant lymphopaenia did not appear to be a major adverse event in the original study [51], with only 1% of participants experiencing a grade IV lymphopaenia (absolute lymphocyte count <200cells/mm¬¬3), and normalisation occurring within 2 months of discontinuation [48]. The German group's findings support this, with lymphopaenia affecting 38.1% of their enrolled participants, however only resulting in treatment discontinuation in a minority [50].

The long-term development of hypertension in an older population with siponimod use, occurred in 16.2% of the 227 pwSPMS in the German study [50], and potentially greater risk of macular oedema in the context of diabetes, uveitis, or other underlying retinal disease [52].

The cardiac safety profile of siponimod from EXPAND was favourable compared to fingolimod [51], with only a small mean decrease in heart rate (by 3.1 beats/minute) by 7 days being seen, and no second- or third-degree heart block on telemetry lasting up to 6 days.

The AMASIA study is a German prospective non-interventional observational study, assessing the long-term effectiveness and safety of siponimod in routine clinical use for SPMS. It is running across 250 sites, was initiated in 2020, and is due to conclude in 2025 [59]. Ultimately, though it is unclear when siponimod should be discontinued, the Canadian agency for drugs and technologies in health recommends discontinuation if the EDSS reaches 7 (i.e., being wheelchair bound), or if there is a worsening of timed-25-foot walk of ≥20% while on siponimod [60].

As lymphopaenia was the most common side effect [50], it's important to be aware of the recommended management steps; should an absolute lymphocyte count drop below 0.2 x 109/l, the dose should be reduced from 2mg to 1mg, and if persistent, treatment should be interrupted until counts recover to 0.6 x 109/l before considering re-initiation [52]. The management of hypertension should also be considered, but broadly speaking this would involve weighing a risk/benefit decision regarding continuing siponimod, and then (via GP) typically initiating either an angioten-

Table 2. Siponimod side effects of note (from Electronic Medicines Compendium, 2023a)

Very Common (≥1/10)	Hypertension
Common (≥1/100 to <1/10)	Herpes zoster Basal cell carcinoma Lymphopaenia Macular oedema Convulsions Tremor Bradycardia Atrioventricular (1st and 2nd degree) block Pulmonary function test dysfunction Liver function test derangement

Table 3. Ocrelizumab adverse events from Schweitzer et al., 2019

Most important events	Risk with age
HSV1/VZV reactivation	Increased
HBV	Increased
Breast cancer	Increased
Hypogammaglobulinaemia	Potentially increased
PML (carry over)	Potentially increased

sin-converting enzyme inhibitor or angiotensin II receptor blocker in those under the age of 55 years, or a calcium channel blocker in those aged 55 or over or of African/Caribbean descent [61].

Ocrelizumab for PPMS

Ocrelizumab is a humanised anti-CD20 antibody that depletes mature and immature B cells, while sparing long-lived CD20-negative plasma cells [62].

The ORATORIO trial demonstrated efficacy in active primary progressive MS in 2017 [63], reducing rates of 12-week CDP over a 120-week period against placebo (24% reduced HR), with subgroup analyses supporting its benefit on 12-week CDP in patients with gadolinium-positive scans at baseline (35% reduced HR), resulting in approval for its use in the UK in 2019 [64]. The risk profile is clearly described (highlighted in Table 3) and is shared with B-cell depleting therapies (BCDTs) [65].

Studies have suggested that being ≥60 years old confers greater risk of hypogammaglobulinaemia, neutropaenia, and infections generally [66,67]. Concerns of immunosuppression have been highlighted by case reports of severe infections in patients over the age of 70 with rituximab related hypogammaglobulinaemia that could not be controlled with antimicrobial therapy [68], increased rates of herpetic reactivation [69], and loss of historic immunity to VZV [70]. This is supported by data demonstrating a greater risk of severe COVID19 outcomes in pwMS on ocrelizumab, as well as older ages, males with comorbidities, greater disability, and a longer duration of MS diagnosis [71,72]. Similarly, the use of ocrelizumab has been found to result in lower seroconversion and humoral immunity response rates following COVID19 vaccination [55,73].

There have been 12 reported cases of PML in pwMS while on ocrelizumab (reflecting 0.00005% of the worldwide population on ocrelizumab, or 1/20, 833 cases) [74,75], 10 of which were attributed to a cross-over effect, having occurred up to several months following conversion from a previous drug that was known to increase the risk of PML, with similar findings in rituximab [30]. The remaining two cases had no history of immunosuppression or use of immunosuppressants; one patient was in their fifties, and the other in their seventies with an underlying immunosenescence and low pre-ocrelizumab lymphocytes count. Ultimately both individuals died from PML-related complications [74].

The ORATORIO trial demonstrated a non-significant increase in the number of malignancies in patients treated with ocrelizumab (11/486 cases, 2.3%, versus placebo 2/239 cases, 0.84%) [63]. Assessment of all trial data by Genetech of the breast cancer risk also shows a non-significant increase in rates of females treated with ocrelizumab (6/781, 0.77%, versus 0/668 controls treated with Rebif or placebo [74]. However, the rate was within the background rate expected for an MS population, which is important to consider in the context of individual cancer risks. Similarly, BCC incidence appeared to be greater between years 3-4 of treatment, but this was not sustained in subsequent years and again was in keeping with background MS rates (Schweitzer et al., 2019; Electronic Medicines Compendium, 2023).

A large German prospective non-interventional observational study, CONFIDENCE, for 3,000 RRMS and PPMS treated with ocrelizumab launched in 2020 and will provide significant long-term real world safety data [77].

Alternative and Emerging Potential Treatments

Treatment regulation varies between countries; it is helpful to be aware that most treatments available for RRMS are also options in active PMS in other countries, such as the United States of America (USA) [78]. Among those is the Federal Drug Association (FDA) licensed Ofatumamab, a fully human anti-CD20 monoclonal antibody and BCDT [79]. The phase 3 ASCLEPIOS I and II trials involved both pwRRMS and active SPMS, and showed, compared to Teriflunomide, a reduction in annualised relapse rates (0.11 versus 0.22) and lower 3-month CDP (HR 0.68) [80], with only a limited increase in serious infections (2.5% versus 1.8%) [80], and sustained safety evidence in the 4-year ALITHIOS study and phase 2 MIRROR study in pwRRMS [81]. Specifically, the ALITHIOS study showed no increase in infection rates by exposure duration, episodes of opportunistic infection, hepatitis B reactivation, or PML [82,83]. Similarly, there was no evidence of increased neoplasm rates, or clustering of malignancies in the original study, and the follow up 4-year safety data identified malignancies in 11 patients (0.6%), with no increase

Table 4. Investigation and management of select condition

Condition	Manifestations	Pre-treatment screening/management	Work-up	Management
Secondary Hypogammaglobulinaemia [83 – 88]	● Recurrent infections ● Recurrent *Streptococcus pneumoniae*, or *Haemophilus influenzae* infection ● Opportunistic infections	Can consider FBC, IgG, IgA, and IgM levels where relevant	● FBC ● IgG, IgM, IgA levels ● Consider IgG subclasses	Cessation of treatment should be considered, alongside active treatment of concurrent infection with a bacterial agent. Can consider: ● IVIg 400-600mg/kg depending on IgG level. ● Long-term antimicrobials ● CT-chest
HSV [89 – 90]	Oral or genital herpes	N/A	Not typically required but in the event of diagnostic uncertainty or initial treatment failure can consider: ● Viral swab PCR ● Viral culture, ● Serological testing gG1 / gG2	Treatment within 48 – 72 hours of onset with a 5 – 10-day course of either oral: ● Acyclovir 400mg x5d ● Valacyclovir 1g BD ● Famciclovir 500mg BD Plus, oral analgesia Can consider: IV foscarnet.
VZV [91 - 93]	Shingles; dermatomal pain and typical papular rash	VZV IgG status Management: ● Vaccination should be performed in cases with either weakly positive or negative titres, prior to treatment initiation. ● In the immunocompromised the recombinant Shivrix vaccine is preferrable	N/A	Treatment within 1w of onset (and up to rash crusting) 7d course of either oral: ● Acyclovir 800mg x5/d ● Famciclovir 500mg TDS ● Valaciclovir 1g TDS Plus, oral analgesia and chamomile lotion N.B: If severe or risk of ocular involvement would require IV treatment at 10mg/kg TDS

in incidence rates over time of exposure, with the only clustering being of BCC (n=4) and invasive breast carcinoma (n=2) [82,83].

Bruton Tyrosine Kinase Inhibitors (BTKi) are a novel drug class of small molecules capable of crossing the blood brain barrier, that have the potential to target both the adaptive and innate immune mechanisms of both the peripheral and central nervous system [84]. Multiple agents are undergoing phase 3 trials currently, however phase II and extension safety data has been largely reassuring with the most common reported events being upper respiratory tract infections, headache, and raised liver enzymes [84].

The MS-STAT2 trial, investigating the effect of high-dose (80mg) simvastatin in pwSPMS is due to conclude in late-2024 [85]. Simvastatin is a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor, with PMS-relevant properties [86], and directly effects vascular co-morbidity, which has been shown to influence PMS outcomes [87]. Its benefit and safety profiles are well recognised from its common use in vascular diseases [88], which has been mirrored in safety data from the MS-STAT1 trial [89].

Lastly, an in depth summary of the trials landscape in progressive MS has recently been published, which further details the above alongside other completed and ongoing PMS trials [90].

Select Treatment Considerations

Among the described treatment options certain complications arise with greater frequency and therefore prophylactic considerations or management is worth elaborating on; this is summarised in Table 4 below.

There has been an intense development in our understanding of vaccination success in patients with MS on DMTs since the COVID19 pandemic, it is worth noting the importance of seasonal influenza vaccination generally, and the administration of the 23-valent pneumococcal polysaccharide vaccine (PPV23), in those on long-term immunosuppressive therapy. PPV23 should ideally be administered at least 2 weeks before initiation of maintenance immunosuppressives, and is also recommended for those established on treatment [91,92]. In those already established on ocrelizumab, which can particularly impair the humoral response, antibody titers can be considered to assess whether repeat vaccination is required [93].

Conclusion

In summary, the use of INF- β-1b in relapsing PMS has the most limited risk profile, without convincing evidence of significant adverse effects generally, or infections/cancer specifically – however the evidence of gain from a clinical progression viewpoint is limited, and in the UK is rarely used.

When prescribing siponimod it is important to primarily weigh up the potentially increased risks of herpetic reactions, reduced vaccination efficacy, BCC, hypertension, and macular oedema, in the context of age-related risks. The risk profile for ocrelizumab is greater, with more risk of immunocompromise, severe infection outcomes, impaired vaccine responses and the potential to lose historic immunity, however the cancer risk is less convincing at present and requires a more nuanced approach to an individual's history.

Ultimately, larger prospective observational data, such as from AMASIA for siponimod and CONFIDENCE for ocrelizumab, are needed to better guide decision making, with planned completion in 2025 and 2028 respectively. In the interim, an open discussion about the above potential benefits, reduced likelihood of DMT impact, and shift in risk profiles with advancing age, needs to be had in order to reach a care decision that takes into consideration an individual's views and opinions on the potential risks and benefits of continued treatment.

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