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Highlights

- Disease-modifying therapies (DMTs) have transformed outcomes in multiple sclerosis
- Many DMTs used in multiple sclerosis (MS) are biologic medicines
- In other therapy areas, biologics have been succeeded by biosimilar medicines
- Biosimilar medicines may provide a cost-effective alternative to biologic MS DMTs
- Appropriate education is key for successful adoption of biosimilar medicines

A place for biosimilars in the changing multiple sclerosis treatment landscape

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Abstract

Background: The treatment paradigm for multiple sclerosis (MS), particularly relapsing-remitting MS, is heavily reliant on biologic disease-modifying therapies (DMTs). However, the current cost of treatment acts as a significant barrier to access for patients. Over the next few years exclusivity periods for key biologic medicines used in MS are likely to end, opening the door for biosimilar medicines to enter the market.

Methods: In this review, we discuss what biosimilar medicines are, and how the existing experience with biosimilar medicines across multiple therapy areas can inform the assimilation of biosimilar medicines into the MS treatment landscape in Europe and the US.

Results: There is currently a lack of knowledge and awareness around the distinctions and similarities between small molecules, non-biological complex drugs, and biological medicines, as well as the different categories of follow-on successor medicines. These include biosimilar medicines that offer a matching efficacy and safety profile to the reference biologic. Understanding and recognition of the stringency of the approval pathways required for drug categories such as biosimilars are key in building confidence in treatment outcomes. For example, biosimilar medicines are sometimes perceived only as 'copies' of their reference biologic despite undergoing an extensive approval process requiring that no clinically meaningful differences are observed between the biosimilar medicine and the reference medicine.

For MS, introduction of biosimilar medicines in the future will enable more people with MS to receive effective treatment, and also expand access to biologic DMTs in MS. Experiences from the use of biosimilars in multiple therapy areas have shown us that this can result in cost-saving benefits for a healthcare system. Introduction of biosimilar medicines in other therapy areas has also demonstrated the importance of appropriate, accurate education and information for their successful integration into clinical practice.

Conclusion: In order to realize optimized treatment outcomes in MS in coming years and to find the appropriate place for biosimilar medicines in the changing MS landscape, it is essential that clinicians and people with MS understand the fundamentals of biosimilars, their potential benefits and consistency of treatment provided by a biosimilar medicine, given the matching efficacy and safety profile to its reference medicine. As evidenced in other therapy areas, biosimilar medicines may reduce key barriers to access by providing a cost-effective alternative to the MS treatment arsenal, while providing the same treatment outcomes as reference biologics.

Keywords

Multiple sclerosis, biologic, biosimilar, access, costs, patient care

1. Introduction: The evolution of treatment options in multiple sclerosis (MS)

MS is a chronic inflammatory disease, typified by central nervous system lesions that can lead to severe physical, cognitive, and other neurological defects (Ghasemi et al. 2017; McGinley et al. 2021). Symptoms may intensify and subside between relapses and periods of apparent clinical stability (Reich et al. 2018; Owens. 2016). Patients endure a clinical burden, and patients, families and caregivers, employers, and the healthcare system carry the substantial economic burden associated with the disease for many years (Owens. 2016).

Treatment for MS was revolutionized with the advent of disease-modifying therapies (DMTs), beginning with the approval of a biologic medicine – injectable interferon-beta – in the 1990s (Madsen. 2017). Interferons provided an immunomodulatory option for a disease that, until then, had been largely treated symptomatically with corticosteroids (Madsen. 2017). Approval of interferons opened the floodgates for development of biologic medicines, non-biological complex drugs (NBCDs) and small molecule medicines to address the immune dysfunction present in MS and attempt to slow the effects of neuro-inflammation on the brain (**Table 1**).

In patients with relapsing MS, DMTs are used to reduce relapse rate, mitigate relapse-associated worsening, and slow disability progression (Gholamzad et al. 2019; Dobson and Giovannoni. 2019). Long-term disease remission has been reported in some patients receiving aggressive immune reconstitution therapy (Muraro et al. 2017), but there is currently no definite cure for MS (Gholamzad et al. 2019). Despite the advances of the past 30 years, access to effective treatment is still difficult for many patients. While DMTs have revolutionized healthcare, the cost of biologic medicines represents a major barrier preventing uniform access to treatment (McCamish et al. 2016). Furthermore, despite an increase in DMT diversity in the US in recent years, acquisition costs for all DMTs have escalated at much higher rates than would be expected due solely to medical inflation (Hartung. 2017) (see section **4.1**).

Table 1: DMTs approved by FDA/EMA for treatment of MS at the time of publication

Medicine	Type	Mechanism of action	Date of authorization	Indication	Successor/ follow-on medicine available*
Alemtuzumab (*Lemtrada*®; Sanofi Genzyme, PI 2022; SmPC 2022)	Biologic	CD52-directed cytolytic monoclonal antibody	EMA: 2013	Single DMT in adults with highly active RRMS despite a full and adequate course of treatment with ≥1 DMT OR in rapidly evolving severe RRMS defined by ≥2 disabling relapses in 1 year, and with ≥1 Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	No
			FDA:2001	Relapsing forms of MS. Because of its safety profile, use should generally be reserved for patients who have had an inadequate response to ≥2 drugs indicated for treatment of MS	
Cladribine (*Mavenclad*®; FDA. 2019a; Merck. PI 2019; SmPC 2022)	Small molecule	Purine antimetabolite	EMA: 2021	Adult patients with highly active relapsing MS as defined by clinical or imaging features	No
			FDA:2019	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults. Because of its safety profile, use is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for treatment of MS	
Daclizumab (*Zinbryta*®; Biogen, PI 2017; SmPC 2018)	Biologic	CD25 directed interleukin-2 receptor blocking antibody	EMA: 2016 Withdrawn 2018†	Adult patients with relapsing forms of MS who have had an inadequate response to ≥2 DMTs, and for whom treatment with any other DMT is contraindicated or otherwise unsuitable	-

Medicine	Type	Mechanism of action	Date of authorization	Indication	Successor/ follow-on medicine available*
			FDA: 2016 Withdrawn 2018[a]	Adult patients with relapsing forms of MS. Because of its safety profile, use should generally be reserved for patients who have had inadequate response to ≥2 drugs indicated for treatment of MS	
Dimethyl fumarate (*Tecfidera*®; Biogen, PI 2022; SmPC 2022)	Small molecule	Mechanism of action thought to be primarily mediated through activation of the Nrf2 transcriptional pathway	EMA: 2014	Adult patients with RRMS	Yes
			FDA: 2013	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Diroximel fumarate (*Vumerity*®; Biogen, PI 2022; SmPC 2022; FDA. 2019b)	Small molecule	Acts via the metabolite, monomethyl fumarate, mediated partly via activation of the Nrf2 pathway	EMA: 2021	Adult patients with RRMS	No
			FDA: 2019	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Fingolimod (*Gilenya*®; Novartis, PI 2019; SmPC 2021)	Small molecule	Sphingosine 1-phospate receptor modulator	EMA: 2011	Single DMT in highly active relapsing-remitting MS in adults and pediatric patients aged ≥10 years	Yes
			FDA: 2010	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in patients ≥10 years of age	
Glatiramer acetate (*Copaxone*®; Teva, PI 2022; SmPC 2022)	Non-biological complex drug	Mechanism of action is presumed to involve modulation of immune processes	EMA: 2003	Relapsing forms of MS	Yes
			FDA: 1996	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Interferon-beta 1a and 1b (*Betaseron*®; Bayer, PI 2021; *Betaferon*® SmPC 2021; *Avonex*®; Biogen,	Biologic	Unknown	EMA: 1995–1998	Patients with a single demyelinating event with an active inflammatory process, if severe enough to warrant treatment with IV corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS OR patients with RRMS and ≥2 relapses	Yes

Medicine	Type	Mechanism of action	Date of authorization	Indication	Successor/ follow-on medicine available*
SmPC 2021; PI 2021; *Rebif*®; Merck, SmPC 2021; *Rebif*® EMD Serono, PI 2021)				within the last 2 years OR patients with SPMS with active disease, evidenced by relapses	
			FDA: 1993–1996	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Mitoxantrone (FDA. 2000; Hospira Inc., PI 2021; SmPC 2016)	Small molecule	DNA-reactive agent intercalated into DNA through hydrogen bonding, causing crosslinks and strand breaks	EMA: 2015	Highly active relapsing MS associated with rapidly evolving disability where no alternative therapeutic options exist	Yes
			FDA: 2000	For reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary(chronic) progressive, progressive relapsing, or worsening RRMS (i.e. patients whose neurologic status is significantly abnormal between relapses)	
Monomethyl fumarate (*Bafiertam*®; Banner Life Sciences, PI 2021; FDA 2020)	Small molecule	Shown to activate the Nrf2 pathway	-		No
			FDA: 2020	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Natalizumab (*Tysabri*®; Biogen, SmPC 2022; PI 2021)	Biologic	Binds to α4β1integrin, blocking interaction VCAM-1,preventing transmigration of leukocytes across the endothelium into inflamed parenchymal tissue	EMA: 2006	Single DMT in adults with highly active RRMS for patients with highly active disease despite a full and adequate course of treatment with at least 1 DMT OR patients with rapidly evolving severe RRMS defined by ≥2 disabling relapses in 1 year, and with ≥1 Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	No

Medicine	Type	Mechanism of action	Date of authorization	Indication	Successor/ follow-on medicine available*
			FDA: 2004	Monotherapy for the treatment of patients with relapsing forms of MS […] generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy	
Ocrelizumab (*Ocrevus*®; Roche, SmPC 2021; PI 2021)	Biologic	Selectively targets CD20-expressing B cells	EMA: 2021	Adult patients with relapsing forms of MS with active disease defined by clinical or imaging features OR adult patients with early primary progressive MS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity	No
			FDA: 2017	1. Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults 2. Primary progressive MS in adults	
Ofatumumab (*Kesimpta*®; Novartis, SmPC 2021; PI 2020; AMJC 2020)	Biologic	Binds to CD20, inducing lysis of CD20+ B cells primarily through complement-dependent cytotoxicity and, to a lesser extent, through antibody-dependent cell-mediated cytotoxicity	EMA: 2021	Adult patients with relapsing forms of MS with active disease defined by clinical or imaging features	No
			FDA: 2020	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Ozanimod (*Zeposia*®; Bristol Myers Squibb, PI 2022; SmPC 2022)	Small molecule	Sphingosine 1-phosphate receptor modulator	-	Adult patients with RRMS with active disease as defined by clinical or imaging features	No
			FDA: 2020	Treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Ponesimod (*Ponvory*®; Janssen-Cilag, SmPC 2021;	Small molecule	Sphingosine 1-phosphate receptor modulator	EMA: 2021	Treatment of adult patients with relapsing forms of MS with active disease defined by clinical or imaging features	No

Medicine	Type	Mechanism of action	Date of authorization	Indication	Successor/ follow-on medicine available*
PI 2021)			FDA: 2021	Treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Siponimod (*Mayzent*®; Novartis, PI 2022; SmPC 2022)	Small molecule	Sphingosine 1-phosphate receptor modulator	EMA: 2021	Treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity	No
			FDA: 2019	Treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Teriflunomide (*Aubagio*®; Sanofi Genzyme, PI 2022; SmPC 2022)	Small molecule	Selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase	EMA: 2013	Treatment of adult patients and pediatric patients aged ≥10 years and older with RRMS	Yes
			FDA: 2012	Treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	
Ublituximab (*Briumvi*®; TH Therapeutics, PI 2022; SmPC 2022)	Biologic	CD20-directed cytolytic antibody	-		No
			FDA: 2022	Treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	

Information correct at time of publication.
*EMA. 2023. Weinstock-Gutman et al. 2017; Dumitresco et al. 2021; EMA 2017. EMA. 2021b.
†Daclizumab was voluntarily withdrawn by Biogen and AbbVie in March 2018 following reports of serious inflammatory brain disorders in 12 patients (Lancet Editorial. 2018).

CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; Gd, gadolinium; MRI, magnetic resonance imaging; IV, intravenous, nrf2, nuclear factor (erythroid-derived 2)-like 2; PI, prescribing information; RRMS, relapsing-remitting multiple sclerosis; SmPC, summary of product characteristics; SPMS, secondary progressive multiple sclerosis; VCAM-1, vascular cell adhesion molecule-1.

Successor (also referred to as 'follow-on') medicines may offer a cost-effective alternative in MS. Subsequent-entry ('generic') NBCDs (e.g. glatiramer acetate) and generic small molecules (e.g. dimethyl fumarate; fingolimod) have already been approved for MS in the US and Europe (**Table 1**). Regionally developed successor interferons are being used for MS in Mexico, Argentina, Uruguay, Iran, India, and Russia (Rivera. 2019; Meher et al. 2019; Moghadasi 2021), but at the time of publication, a biosimilar DMT has yet to be approved in MS by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, several DMTs are nearing or have passed the end of their exclusivity periods, sparking interest in the forthcoming entry of new biosimilar and generic medicines into the US and European markets.

Biosimilar medicines, similarly to generic medicines, can provide alternative treatment options to branded reference biologic medicines. But while generics are used to interchange with small molecules and are chemically synthesized, branded biologic and biosimilar medicines are large, complex proteins, produced in living cells. Biosimilars have the same amino acid sequence, route of administration and strength as their reference biologic. Because of inherent variability of biologics and their manufacturing processes, both biologics and biosimilars display a certain degree of variability, even within or between different batches of the same medicine, and therefore may have different glycosylation patterns *(*EMA. 2019, Schiestl et al. 2011).

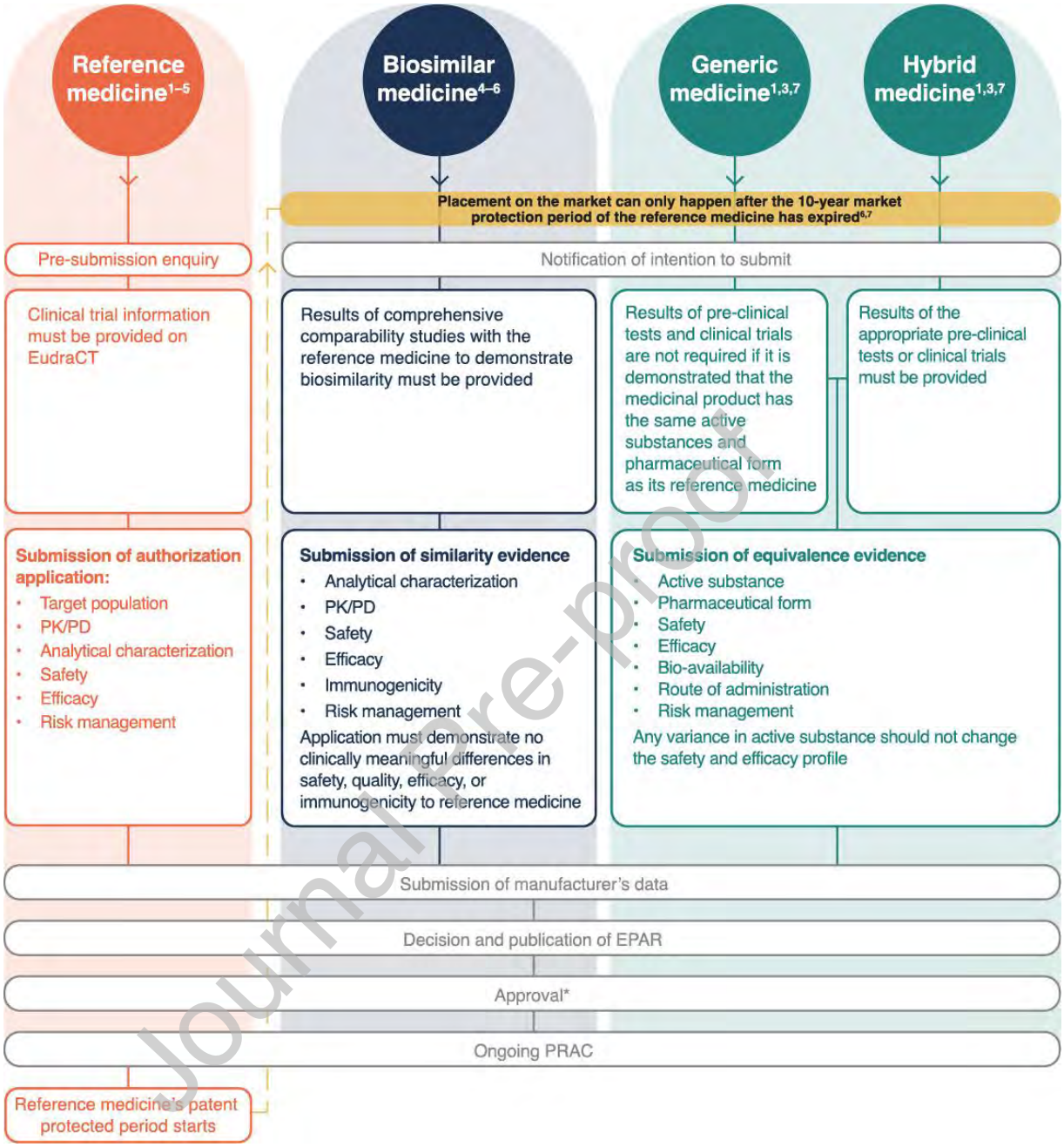
Biosimilar medicines may be of particular relevance, given that biologic medicines form the backbone of high-efficacy treatment in MS. To facilitate acceptance of biosimilar medicines, there is a need for greater understanding around the utility and robustness of successor medicines in MS. The purpose of this review is to provide an overview of what biosimilars are and how they are developed. Further, we will discuss some of the barriers to treatment in MS, and explore, using learnings from their use in other therapy areas, how biosimilar medicines may support future treatment optimization in MS.

2. Differentiating and defining classes of DMTs and successor medicines

MS DMTs include biologic medicines, NBCDs, and small molecules (Table 1). Biologic medicines are large, complex molecules, often proteins (e.g. monoclonal antibodies) (Zhao et al. 2012). Biologics share several characteristics with NBCDs, with a key difference that biologics are derived from living organisms (Zhao et al. 2012), while NBCDs are synthetically manufactured (Crommelin et al. 2015). Both biologics and NBCDs are distinct from small molecule drugs, which are low molecular weight compounds (<1 kDa; 20–100 atoms) commonly produced by chemical synthesis (Zhao et al. 2012; European Commission. 2013).

A biosimilar medicine is a successor to a reference ('originator' or 'original-brand') biologic medicine for which the patent and exclusive marketing rights have expired (EMA. 2019). The EMA was first to define a specific framework for biosimilar approval (Schiestl et al. 2017), which takes place through a centralized procedure, following the same rigorous standards of quality, safety, and efficacy that apply to all biologic medicines (EMA. 2019). The first biosimilar medicine authorized for use by the EMA was a biosimilar somatropin for growth hormone deficiency (Omnitrope®; Sandoz) in 2006 (Schiestl et al. 2017). In the US, a biosimilar abbreviated licensure pathway was created in 2010 as part of the Biologics Price Competition and Innovation Act, applying the same approval standard as for reference biologic medicines (Brill and Robinson. 2020; FDA. 113820. 2022.). The first FDA-approved biosimilar medicine was a biosimilar filgrastim for prophylaxis of chemotherapy-induced neutropenia (Zarxio®; Sandoz), in 2015 (Zarxio® PI. 2021; Brill and Robinson. 2020). At the time of writing, EMA has approved 88 biosimilars (GaBI. 2022) and FDA, 37, (FDA. 2022d), although only a small proportion of FDA-approved biosimilar medicines have subsequently been brought to market (GaBI. 2021a). According to Goode and Chao (2022) and Moorkens et al. (2020), one of the major barriers to bringing biosimilars to market in both the US and EU, respectively, are complex 'patent thickets' surrounding the reference biologic that persist even after the loss of exclusivity.

Due to the specific nuances between the definition and approval pathways of different medicines, concerns may arise that a hierarchy of efficacy/suitability exists between reference medicines and their successors. However, all successor medicines approved for use in Europe and the US require robust evidence of therapeutic effectiveness and equivalence to a reference medicine via distinct, rigorous, and well-defined regulatory processes (**Figure 1a: EMA** and **Figure 1b: FDA**). Recent European consensus guidelines have declared that follow-on DMTs such as biosimilars and NBCDs, when approved within highly regulated areas, can be considered as effective and safe as the reference medicine (Brownlee et al. 2022).



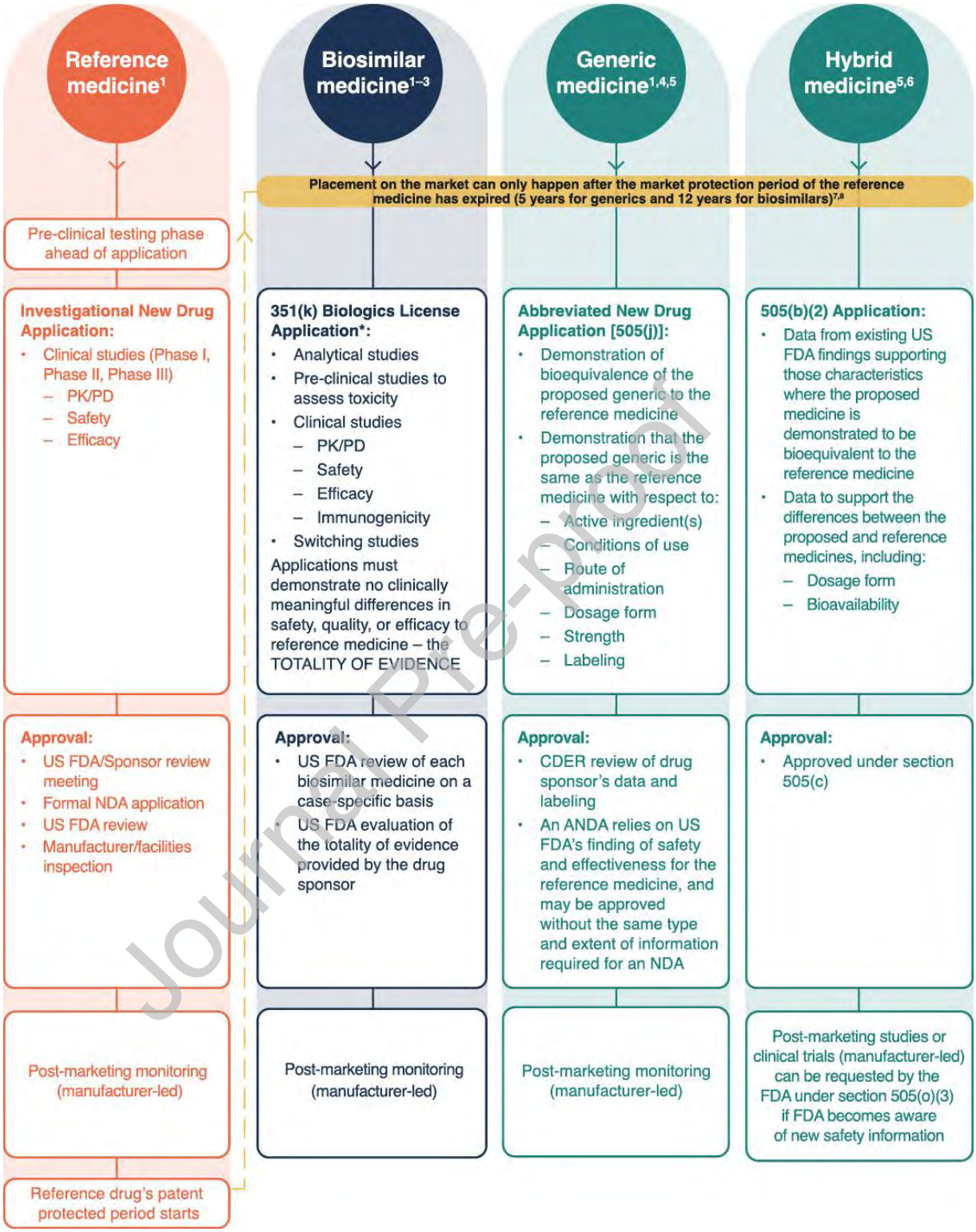


Figure 1: Development steps for generics, NBCDs and biosimilar medicines in comparison to reference medicines. A) EMA; B) FDA.

In brief, small molecule generic medicines are chemically synthesized to have the same active substances and pharmaceutical form as their reference medicine (European Parliament. 2001), with bioequivalence to the reference demonstrated through appropriate bioavailability studies (EMA. 2012).

The complexity of biosimilar medicines means that the development approach for generic small molecules is insufficient to demonstrate similarity. Instead, biosimilars are assessed via a comprehensive comparability approach (EMA. 2014). A biosimilar must match its reference medicine in terms of quality, safety, efficacy, and immunogenicity (Dutta et al. 2020; EMA. 2019). Tailored development programs use existing data for the reference medicine to support approval of the proposed biosimilar (EMA. 2019; FDA. 113820. 2022.). Biosimilar programs aim to demonstrate no clinically meaningful differences in safety and efficacy between the proposed biosimilar and its reference medicine, rather than establishing *de novo* safety and efficacy for the proposed medicine (EMA. 2019; FDA. 113820. 2022.).

Biosimilarity is demonstrated by the 'totality of evidence', encompassing structural, functional, and pharmacokinetic/pharmacodynamic equivalence, and clinically confirmed similarity in efficacy, safety, and immunogenicity in a sensitive population (Markus et al. 2017). As all biologic medicines, including biosimilars, may elicit undesirable immune responses that can impact clinical efficacy and safety, a head-to-head immunogenicity assessment of a proposed biosimilar versus the reference medicine is a critical component of a biosimilar clinical development program (Schreitmüller et al. 2019). The epoetin experience of the 1990s and early 2000s serves as an example of the impact that small manufacturing changes for a biologic and/or biosimilar may have on relative potency and safety (Brinks et al. 2011; Kalantar-Zadeh. 2017), and speaks to the importance of long-term pharmacovigilance programs as recommended in recent consensus guidelines (Brownlee et al. 2022).

Successor NBCDs occupy a separate developmental space to generic small molecules and biosimilars. When a successor medicine does not meet the definition for a generic,

or if bioequivalence to a reference medicine cannot be demonstrated through bioequivalence studies alone due to differences in active substance, strength, indication or pharmaceutical form (European Parliament. 2001; FDA. 2019c), further pre-clinical or clinical trials are required in addition to bioequivalence data (European Parliament. 2001; FDA. 2019c) and the successor medicine is described as a 'hybrid' (EMA. 2022c). In Europe, biosimilar, generic and hybrid regulatory pathways have all been previously used in successor NBCD applications (Gaspar RS, et al. 2020).

3. How DMTs impact treatment goals in relapsing-remitting multiple sclerosis (RRMS)

The 2021 consensus statement of the German Multiple Sclerosis Therapy Consensus Group describes the aim of treatment in MS as '*the best possible disease control and the best possible quality of life (QoL) for the patient*' (Wiendl et al. 2021).

Treatment options for progressive MS unfortunately remain limited, however, multiple DMTs are indicated for RRMS (**Table 1**) and can be considered to occupy different positions along an efficacy and tolerability continuum from moderate (e.g. interferon-beta glatiramer acetate, dimethyl fumarate, teriflunomide) to high efficacy treatments (alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, siponimod, ozanimod, ofatumumab) (Rotstein and Montalban. 2019; Filippi et al. 2022), although exact positioning along this theoretical continuum may vary by assessment criteria (Rotstein and Montalban. 2019; Samjoo et al. 2021).

Recent reviews and cohort studies lend support to the benefit of initiating treatment with highly effective 'induction' or 'early intensive' therapy ('flipping the pyramid') versus guideline escalation-type approaches (Montalban et al. 2018) with the aim of taking advantage of the treatment 'window of opportunity' in RRMS and maximizing long-term outcomes (Harding et al. 2019; Brown et al. 2019; Stankiewicz & Weiner. 2020; Smith Simonsen et al. 2021).

4. Barriers to achieving optimized treatment with high-efficacy DMTs

4.1 Treatment costs

The varied and unpredictable nature of MS, as well as the associated financial costs of treatment, means that, in practice, optimized management may be challenging. A key barrier to implementation of (early) use of high-efficacy DMTs is the high direct healthcare costs associated with such treatments. The 'barrier to remission' is not the existence of the medicine, but whether a given patient is able to access that medicine. DMTs are the primary drivers of healthcare costs after diagnosis in MS, particularly in early disease, and with higher costs reported in patients with RRMS compared with primary progressive MS (Hartung. 2017; Kobelt et al. 2017; Gyllensten et al. 2019).

In the US, annual price increases for most DMTs have exceeded 10% annually (Hartung. 2021), with a typical DMT for MS reportedly costing over $90,000 USD per year (Hartung. 2021) and newer DMTs have entered the market with a cost 25–60% higher than existing DMTs (Hartung. 2015). Annual Medicaid reimbursement in the ten years to 2018 increased by 633%, from $172 million to $1.26 billion (Elsisi et al. 2020). To reduce costs, US insurance companies acting through pharmacy benefit companies may restrict access to DMTs through tiered coverage and/or other policies (Bourdette et al. 2016). It should also be noted that these are *acquisition* costs. If the additional clinical administration time and financial burden of treatment management (e.g. out-of-pocket costs) are included here, the total cost is likely far higher in the US.

The issue of cost extends to Europe: an Italian database analysis of RRMS treatment costs between 1997–2017 reported that annual costs per patient (DMT prescription and management) increased by 11.2% after the introduction of natalizumab in 2007, by 10.9% after the introduction of oral medication in 2011 (fingolimod, teriflunomide and dimethyl fumarate), and by 10.7% after the introduction of alemtuzumab in 2015 (Petruzzo et al. 2020). The need to improve access via reduced cost is experienced

throughout the world, and thus, health ministries play a significant role in the decision to utilize biosimilars.

4.2 Regional variations in treatment access

In Europe, the approach to treatment and care varies substantially between and within countries, meaning some who may benefit from DMTs may not be able to access appropriate treatment (EMSP. 2011). In a 2019 survey commissioned by the UK MS Society, it was reported that only 3 of every 5 people who could benefit from a DMT were currently receiving such treatment (MS Society. 2019).

It could be argued that, ultimately, treatment algorithms are economically driven. A previous World Health Organization (WHO) analysis of worldwide data from the Atlas of MS 2013 found that only half of those eligible for a DMT reported having received one, with reimbursement policy reported as a barrier in 57.7% of responses (Kanavos et al. 2016). This issue is not unique to MS. In rheumatoid arthritis, for example, it has been reported that pharmacoeconomic evaluations and payer policies should be optimized to support biosimilar market entry, with non-medical issues (i.e. disparities between treatment guidelines, DMT costs, regional limitations, reimbursement criteria) flagged as potential barriers to uniform patient access to biologics and effective implementation of treatment strategies (Kim et al. 2020).

5. Experience of biosimilar medicines in neurology and MS to date

Some countries have already brought versions of biosimilar medicines to local markets using local regulatory approvals. For example, successor interferons have been licensed in Mexico, Argentina, Uruguay, Iran, India, and Russia (Rivera. 2019; Meher et al. 2019), however, without rigorous challenge of the pharmacological profile and similarity claims versus the reference biologic (Rivera. 2019). Experiences with these medicines have not been without challenges (Rivera. 2019), compounding the need for assessment of biosimilar equivalence in efficacy, safety, and immunogenicity (Cuevas

et al. 2015). Care should be taken to only use the term 'biosimilar' if the medicine meets the definition of WHO and EMA/FDA guidelines, which require direct comparative assessment of the biosimilar and reference biologic to establish comparability in efficacy, safety, and quality (Kang, et al. 2020).

Stricter approval pathways and requirements for biosimilar medicines mean that Europe, Canada, Japan, and the US have yet to see biosimilar medicines approved for use in MS (Rivera. 2019). However, it could be argued that the neurology community has already seen its first high-efficacy biosimilar medicine in the form of rituximab biosimilars used off-label in MS. Rituximab, a biologic medicine indicated across several oncology and autoimmune conditions (excluding MS) (MabThera® SmPC. 2021; Rituxan® Prescribing Information. 2021), is widely used off-label for the treatment of MS (Torgauten et al. 2021; Brancati et al. 2021; Bernttsson et al. 2018). Several rituximab biosimilar medicines are approved for the reference indications for use in Europe and/or the US (including Truxima®, Ruxience®, Riabni®, Rixathon®, and CT-P10 [GaBI. 2021b; Riabni® Prescribing Information. 2020]).

The efficacy and safety of off-label use of Truxima® versus MabThera® in MS was recently compared in a clinical setting, with apparent equivalence reported for the biosimilar against the reference medicine (Perez et al. 2021). Elsewhere, a small retrospective review of off-label use of infliximab biosimilars for neurosarcoidosis (initiation or switch from the reference biologic) also reported no efficacy, safety, or immunogenicity concerns (Riller et al. 2019).

6. What can we learn from the biosimilar experience in other therapy areas?

Biosimilar medicines have been successfully used in Europe and the US for over a decade in oncology, metabolic diseases, gastroenterology, and rheumatology (GaBi. 2022; FDA. 2022). In the six years to 2022, for example, 16 biosimilars were approved by the FDA for use in rheumatoid arthritis (Conran & Moreland. 2022). Using biosimilar rituximab in oncology as a specific example of integrating a biosimilar into practice, the

first rituximab biosimilars (Rixathon® and Truxima®) were approved by the EMA for follicular lymphoma in 2017, based on the totality of evidence derived from a comprehensive comparability exercise with the reference medicine (Otremba et al. 2020).

The indication was then extrapolated to non-Hodgkin's lymphoma and chronic lymphocytic leukemia: subsequent real-world follow-up in German clinical practice demonstrated that rituximab biosimilars were being used across all indications, with 57.3% of cycles in extrapolated indications. Over 24 months, the proportion of biosimilar prescriptions increased from 12.0% to 83.0%, suggesting increasing acceptance of both biosimilar medicines and extrapolation within the German oncology community (Otremba et al. 2020).

Cost savings to both patients and healthcare systems have been reported as a result of biosimilar introduction, as well as facilitating increased patient access to treatments (Kvien et al. 2022). Other experiences have indicated similar benefits of biosimilar integration, including a five-fold increase in daily use of granulocyte colony-stimulating factor (G-CSF) following introduction of biosimilar G-CSF for neutropenia prophylaxis in Sweden, and anecdotal reports of substantial cost savings following UK uptake of biosimilar G-CSF (e.g. estimated £1 million GBP in annual saved purchase costs) (Gascón et al. 2013). Similarly, mean treatment cost per patient significantly decreased after the introduction of biosimilar etanercept for rheumatology in The Netherlands, and an overall increase in number of patients being treated with biologic medicines was seen due to additional available budget (Müskens et al. 2021).

In the US, however, uptake of biosimilar filgrastim was lower than anticipated and trailed behind other countries (Nava-Parada et al. 2020). Barriers included stakeholder perceptions, financial disincentives related to reimbursement, regulatory policies, and operational guidance (Nava-Parada et al. 2020; Yang et al. 2022). However, a 2020 analysis of recent biosimilar medicine launches showed that some (bevacizumab, trastuzumab, rituximab) are expected to reach over 50% market share by the end of

their second market year (IQVIA. 2020), suggesting that the US market has become more receptive to biosimilar medicines in recent years.

6.1 The importance of appropriate education

In addition to the need for supportive policymaking and budgetary guidance, the biosimilar experience in other therapy areas shows us that education is likely to be key to the successful introduction of biosimilar MS DMTs in Europe and the US. Insights from rheumatology have shown that integration of biosimilar DMTs requires all stakeholders (clinicians, pharmacists, patients, patient organizations) to have confidence in biosimilars, and successful adoption and realization of the full cost-saving efficacy of these medicines depends on careful communication to patients (Smolen et al. 2019).

It is likely that current understanding of biosimilar medicines is low, both in the MS community and in the general population. A previous US survey of nurse practitioners and physicians' assistants in gastroenterology (n=76) reported that <6% described themselves as 'very knowledgeable' on the use of biosimilar medicines; 54% 'somewhat knowledgeable' and 41% 'not knowledgeable' (Bernasko et al. 2021), reflecting a perceived lack of relevant education and concerns about the safety and efficacy of a biosimilar by advanced practice providers (Bernasko et al. 2021).

Overall patient awareness of biologic and biosimilar medicines is also seemingly limited. A previous international survey conducted shortly before the FDA's first biosimilar approval reported that awareness of biologic therapies was very low in the general European/US population (10–11%). This rose to 19–30% in patients diagnosed with autoimmune disorders or cancer, and 43–47% in diagnosed patient advocates. Awareness of biosimilar medicines was even lower: 6% in the general European/US population versus 9–11% in diagnosed patients, and 20–30% in diagnosed patient advocates (Jacobs et al. 2016). A more recent Belgian survey indicated that biosimilar knowledge remains low: only 38% of surveyed patients (diagnosed with autoimmune or metabolic disorders) had heard of biosimilar medicines, with their physician, patient

organization or the internet being the primary sources of information (Vandenplas et al. 2022).

6.2 Acceptance of switching

As per the core tenets of biosimilarity, switching should have no significant impact on the patient experience or treatment outcomes. However, the concept of biosimilar switching has occasionally been met with resistance. Previously, criticism has been levelled in oncology and rheumatology at the limited statistical power and design features of biosimilar switching studies, particularly given the potential complexity of real-world switching scenarios (Declerk et al. 2018). Elsewhere, conclusions regarding the 'controversy' around biosimilar switching have been published (Cohen & McCabe. 2020), despite a lack of substantial data to support this perception (Cohen & McCabe. 2020; Wiland et al. 2018). Any biosimilar used in MS would likely be prescribed in both treatment-naïve and switching scenarios. The FDA offers a regulatory pathway considering a designation of interchangeability (FDA. 2019d), while EMA released a joint statement with the Heads of Medicines Agencies in September 2022 to confirm that 'biosimilar medicines approved in the EU are interchangeable with the reference medicine or equivalent biosimilar' (EMA. 2022d).

A key requirement of clear and effective communication around biosimilar medicines is to enable confidence in the process of switching. A recent US survey study of real-world switching experiences for oncologists and patients with breast cancer demonstrated that patients and oncologists were not aligned regarding patient opportunities to ask questions, adequacy of resources, treatment effectiveness, patient worry, and magnitude of change when switching to a biosimilar medicine (Papautsky et al. 2022). Reportedly, 40.8% of patients switched to a biosimilar medicine were not notified in advance. Of those who were informed, information came from the treating clinician (26.4%), advanced practice provider (5.7%), chemotherapy nurse (15.5%), pharmacist (2.9%), or insurer (4.0%); 44% of surveyed patients learned about the new treatment via self-directed learning. Likewise, over half of the surveyed oncologists (54.8%) reported

that they did not receive any manufacturer materials relating to the new biosimilar medicine (Papautsky et al. 2022).

A wealth of data have demonstrated the relative safety of switching to biosimilars. The NOR-SWITCH study – the first government-funded, randomized, double-blind, non-inferiority trial evaluating the impact of switching from reference to biosimilar infliximab – is likely the best-known example (Jørgensen et al. 2017). NOR-SWITCH demonstrated non-inferiority of biosimilar infliximab within a pre-specified 15% margin, with similar safety and immunogenicity outcomes reported across the two groups (Jørgensen et al. 2017). Elsewhere, a review of 53 switching studies for four biologic medicines (infliximab, etanercept, adalimumab, rituximab) across three therapy areas (rheumatology, gastroenterology, dermatology) noted that efficacy, safety, and immunogenicity (where assessed) were, overall, comparable between patients who switched treatments versus those who did not. No differences were seen pre- and post-switch (Moots et al. 2017). Likewise, a recent, exhaustive systematic review of 178 studies reported biologic-biosimilar switch data from real-world data as well as randomized controlled trials in Europe. Design heterogeneity was reported as a consideration, but no robust indications of major efficacy, safety, or immunogenicity issues were identified. Some open-label and observational studies reported increased discontinuation rates after switching, which were mainly attributed to the nocebo effect (see section **6.3**) (Barbier et al. 2020). This review concluded that any outstanding uncertainties associated with a single switch from a reference biologic to a biosimilar medicine are not sufficient to discourage switching (Barbier et al. 2020). Both reviews recognized the need for continuing pharmacovigilance and additional data, such as on multiple switching scenarios (Moots et al. 2017; Barbier et al. 2020), as would be expected for a reference biologic. Recent European consensus guidelines agree that there is a lack of evidence to date relating to multiple and cross-switching scenarios among successor DMTs (Brownlee et al. 2022).

6.3 The nocebo response

As noted above, biosimilar medicines are not well understood by many healthcare professionals (HCPs) and patients, and this knowledge gap has been worsened by disparagement and/or misinformation (both intentional and unintentional), creating a negative perception of the value of a biosimilar in relation to a reference biologic (Cohen and McCabe. 2020). This issue is compounded by confusion around appropriate terminology (Kang, et al. 2020), as evidenced by incorrect classification of NBCDs (i.e. glatiramer acetate) as biologics in the literature (Sabatino Jr et al. 2017; Michels et al. 2020), furthering uncertainty around effectiveness and tolerability of different classes of successor medicines.

The nocebo effect is a common and difficult to quantify artefact in medicine whereby a lack of efficacy and/or adverse events occur due to patients' negative expectations and previous experiences. Investigations into the nocebo effect related to biosimilar and generic use have been heterogeneous, making the true incidence rate of nocebo difficult to evaluate (Spanou et al. 2019; Fleischmann et al. 2020). Nocebo risk can be minimized with education – closing the knowledge gap about generics and biosimilar medicines – to aid HCP and patient understanding and confidence in the value of a medicine, as well as use of tools to recognize risk of nocebo response (Spanou et al. 2019). One narrative review of biosimilar switching in rheumatology and gastroenterology also noted that discontinuation and switch-back rates were higher in studies where patients were not given a treatment choice: forced switching may intensify negative expectations and contribute to therapy discontinuation rate (Fleischmann et al. 2020).

Despite actual or perceived issues, clinical and real-world evidence indicates that appropriate use of approved biosimilar medicines is as effective and safe as their reference medicines, and they have been shown to offer consistent treatment outcomes in treatment-naïve or switching patients across various therapy areas (Moots et al. 2017; Ebbers et al. 2019; Barbier et al. 2020; Piezzo et al. 2021; Macaluso et al. 2022).

For biosimilar medicines to be effective in MS in the future, it is essential that prescribers and patients participate in shared decision-making using accurate information about biosimilar treatment options.

7. How biosimilar medicines could help address the unmet need in MS

7.1 Healthcare savings

The US National MS Society's guiding principle is that '*access to affordable, appropriate, high-quality healthcare is essential for people with MS to live their best lives*' (NMSS. 2021), a sentiment that is shared in the primary action points of the European Multiple Sclerosis Platform (EMSP. 2019).

Biosimilar medicines may represent an option against the barriers to effective high-efficacy biologic therapies, supporting clinicians to provide the most suitable medicine for an individual patient (McCamish et al. 2016), a key need for MS treatment. Biosimilar medicines are generally less expensive to develop than reference biologics, partly due to an abbreviated clinical trial program, and potentially due to a more advanced and efficient production process (Dutta et al. 2020); quality and comparability remains uncompromised versus the reference biologic due to the regulatory rigor of biosimilar approvals (see section 2).

The crucial driver for uptake of a biosimilar medicine is cost reduction relative to the reference biologic (Dutta et al. 2020). In Europe, list-price discounts for a first biosimilar vary by country, e.g. from 5–15% in the UK to 20–45% in Germany, with subsequent biosimilars potentially receiving similar or the same discount (Heredia et al. 2018). US list-price discounts for biosimilar medicines have been reported to reach 35% (12% for Medicaid) (Heredia et al. 2018).

Biosimilar medicines and their reference biologics are expected to compete on price for market share (Mulcahy et al. 2018). In the US, for example, it has been estimated that

use of biosimilar medicines will reduce direct spending on biologic medicines by $54 billion (range: $24–150 billion) from 2017 to 2026, or ~3% of total estimated biologic spending (Mulcahy et al. 2018).

The introduction of the successor NBCD glatiramer acetate in the US may offer a snapshot of the potential savings associated with future introduction of biosimilar medicines. Generic glatiramer acetate was authorized by the FDA in 2015 (Glatopa. Prescribing Information. 2022). Between 2015 and 2019 gross sales for all glatiramer acetate in the US fell from ~$4.5 million to ~$2.5 million while the proportion of glatiramer acetate prescriptions remained consistent (accounting for 33% of total DMT prescriptions in 2015 and 32% in 2019) (Greenberg et al. 2020).

It has been proposed that healthcare systems can make substantial savings if patients are switched to biosimilar medicines, and if biologic-naïve patients are initiated on biosimilar rather than reference medicines (Smolen et al. 2019). In Europe, incentives and policies promote market access for biosimilar medicines to combat restricted healthcare budgets, increases in the burden of diseases, and an aging population (Dutta et al. 2020). In the US, a recent survey of payers and HCPs using biosimilars in oncology reported that up to 87.5% of physicians were using biosimilar medicines in >50% of their treatment-naïve patients and were comfortable using biosimilars but that their role in selecting a biosimilar medicine was minimal; use was largely dependent on practice protocols or insurance preferences. This survey also revealed that the major factor influencing payers' coverage decisions and biosimilar adoption was the potential cost saving (Yang et al. 2022).

In addition to price competition, market data from other disease areas have shown that introduction of biosimilar medicines leads to increased overall use of biologic medicines. Furthermore, widening of prescription options increases access to previously cost-prohibitive treatment and facilitates market competition; allows payers to re-align therapy lines and biosimilar reimbursement; improves processes and patient services; and encourages reference manufacturers to pursue new indications and formulations

(IMS. 2016; Dutta et al. 2020). For MS, introduction of biosimilar medicines could improve affordability of high-efficacy biologic DMTs, allowing for wider distribution of healthcare resources and, potentially, an increase in the number of patients able to receive an appropriate DMT.

7.2 Patient choice and individualized care

Widening a treatment range gives a physician more opportunity to treat with the most suitable DMT and has the potential to allow treatment goals for MS to become more ambitious. A 2021 German registry analysis reported that broader availability of DMTs was associated with an increase in treatment effectiveness for RRMS, with a decrease in annualized relapse rates, reduced disability progression over an 8-year period, and stability of NEDA (no evidence of disease activity) criteria (Braune et al. 2021).

In the future, increasing access to (high-efficacy) induction treatment choices for RRMS via biosimilar adoption may bring significant benefit to clinical and QoL outcomes for people with MS. Availability of biosimilar medicines could facilitate greater adoption of personalized treatment approaches for this heterogeneous disease (Linker and Chan. 2019; Braune et al. 2021). Biosimilar medicines may support overall *earlier* use of biologic therapies (IMS. 2016).

There is also a cost-of-care benefit associated with optimized treatment access in MS. Uncontrolled, or poorly controlled, MS is undesirable for both the patient and the healthcare system. Treatment and care associated with relapses can be substantial drivers of MS clinical costs (O'Connell et al. 2014; Cortesi et al. 2020). A 2021 retrospective US cohort showed total annual all-cause and MS-related costs increased with severity of relapses, reflecting mean MS-related costs of $69,586 versus $43,233 for severe versus mild-moderate relapses, respectively (N=8,775; 25% using a DMT) (Nicholas et al. 2021).

Treatment with a high-efficacy DMT reduces relapse severity (Nicholas et al. 2021), and thus positively impacts the cost of relapse. Excluding the cost of the DMT, medical and non-medical costs for patients on a DMT for MS have been shown to be lower than for those not on a DMT (Nicholas et al. 2020). By extension, availability of biosimilar medicines in MS may support the use of high-efficacy treatments to reduce relapse risk and severity, and reduce cost of care. It is important for patients to understand the science behind the use of biosimilar products. Discussing the development pathway and requirement for human data is critical for patients to understand the reasons supporting the use of biosimilars.

8. Summary

There is an urgent need in neurology for affordable, accessible DMTs to support optimized patient outcomes. In MS, introduction of a biosimilar in treatment class-naïve patients or switch setting could reduce the cost-related barriers to access and support optimized long-term treatment aims via increased or earlier use of first-line high-efficacy DMTs. This is achieved by the use of therapeutics that have the same demonstrated efficacy, safety and mechanism of action.

Biosimilar experiences in other therapy areas should be leveraged to facilitate uptake in a biosimilar-naïve setting. Policies should be optimized to support biosimilar market entry. Patients and all HCPs involved in the prescription of biosimilar medicines require appropriate support and education to empower decision-making, and combat the potential risks associated with misinformation.

The development of a biosimilar is part of the natural cycle of medicine development and should be viewed as such: a patent expires and successors are brought in, while the innovator company seeks new active ingredients, formulations and indications, thus driving innovation. Introduction of a biosimilar medicine may even prolong the use of reference biologic treatments through wider availability and clinician familiarity.

To conclude, biosimilar medicines have proved beneficial for over a decade in oncology, metabolic diseases, gastroenterology, and rheumatology; MS could soon be following in these footsteps. To quote a previous rheumatology perspective, it may be that '*the wind of change'* (Schneider 2013) is now approaching the MS treatment paradigm.

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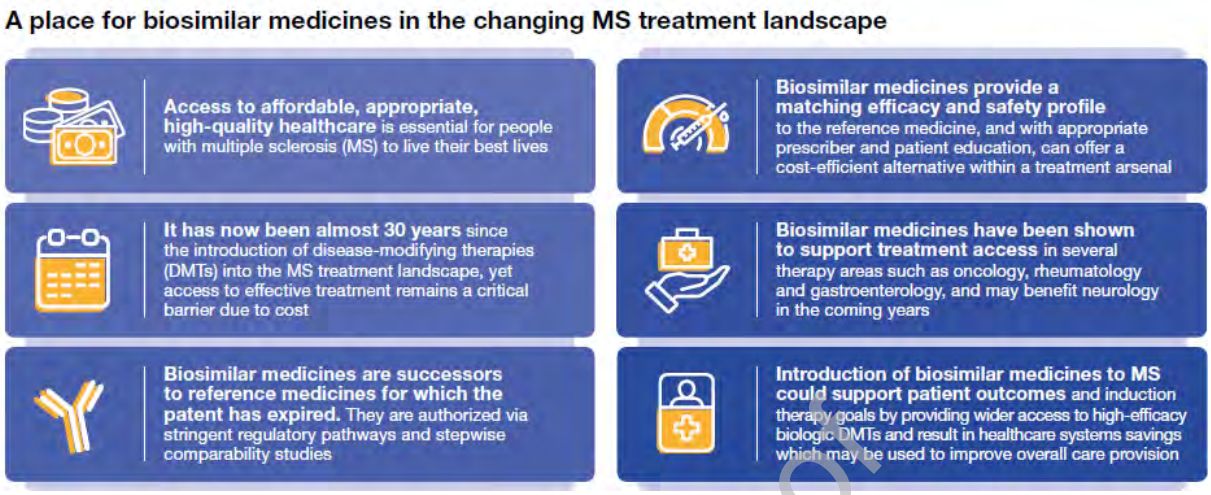
Graphical abstract



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