Considerations in the development of generic disease therapies for multiple sclerosis

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Abstract

Purpose of review: Medication prices are a major contributor to the high cost of care for multiple sclerosis (MS). The patents for some of the initial injectable therapies for relapsing MS recently expired, permitting development, regulatory approval, and marketing of generic alternatives with the potential for lower prices and cost savings to payers and patients.

Recent findings: A generic version of glatiramer acetate 20 mg administered by daily subcutaneous injection recently received regulatory approval in the United States. Two additional generic versions of glatiramer acetate have been submitted for regulatory review. The development and testing of generic disease-modifying therapies for MS such as glatiramer acetate, which are complex molecules, present several complicating factors. **Summary:** This article provides background on the development of generics and reviews the status of generic glatiramer acetate. *Neurol Clin Pract* 2016;6:369-376

As of January 2016, 13 disease-modifying therapies (DMTs) have regulatory approval to treat relapsing multiple sclerosis (MS). The availability of DMTs with different mechanisms of action, potencies, routes of administration, and safety profiles represents major progress in MS management. However, all of these medications are expensive and a major contributor to the high cost of care for MS. Counterintuitively, with the emergence of new DMTs, which would be expected to increase competition, the prices of all MS DMTs have continued to increase.¹ The reasons behind rising cost and potential remedies are complex. Recent expiration of the patents for some MS DMTs permits marketing of generic alternatives with the potential for lower prices and cost savings to payers and patients. However, the development and regulatory approval of generic MS DMTs is not straightforward.

Regulatory aspects of generic drugs

In both the United States and Europe, the overall process of development and approval of generics vs new drugs has important differences (the table provides definitions of key terms).

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Table Key definitions

Term	Definition
Innovator drug	The approved brand medicinal product, also known as the reference product.
Generic	Copy of a brand-name drug that is the same in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.
Biological	Product with an active ingredient produced by or extracted from a biological source.
Biosimilar	Generic version of a biological drug, also known as a follow-on biological.
Complex generic	Generic version of a complex molecular entity, includes both biosimilars and complex nonbiological drugs, which present similar issues.
Interchangeable	Interchangeable is a higher standard than equivalent. It indicates that the generic drug is expected to produce the same clinical result as the reference product in an individual patient, i.e., if administered more than once, the risks in terms of safety or reduced efficacy for switching are not greater than with continued use of the reference product. An interchangeable generic drug can be substituted by a pharmacy for the brand product without authorization of the prescribing health care provider.

For new drugs, 2 pivotal trials generally are required to confirm safety and efficacy. Historically, in MS, this requirement has been addressed by demonstrating superiority compared to placebo but increasingly is vs active comparators (figure 1). In contrast, small molecule generics can be verified as being safe and effective by showing pharmaceutical equivalence (i.e., the same active ingredient, purity, strength, dosage, and route of administration) and bioequivalence (i.e., similar rate and extent of absorption, providing the same exposure) compared to the previously approved brand drug, also known as innovator drug or reference

Figure 1 Comparison of pivotal trials of innovator and generic MS disease therapies

(A) Pivotal trials of innovator drugs seek to show superiority on a clinical endpoint compared to placebo or an active comparator. (B) In contrast, pivotal trials of generic drugs seek to show equivalence of the generic and innovator on a more sensitive imaging endpoint.

Too relaxed requirements may jeopardize efficacy or patient safety. Too stringent requirements create a disincentive to pharmaceutical companies.

product. As a result, only one small trial comparing the pharmacokinetics of the generic and brand drug is required.

Testing generic biological drugs (biosimilars) is more difficult. Due to their more complicated molecular structure, in vitro and animal studies may not predict behavior in humans adequately. Minor changes in the manufacturing process can produce different posttranslational modifications, higher-order structure, aggregation, microheterogeneities, or minor impurities possibly resulting in altered efficacy, toxicity, or immunogenicity with unanticipated consequences, as illustrated by pure red cell aplasia associated with generic erythropoietin.² Therefore, at least one human study typically is expected for biosimilars to assess immunogenicity, pharmacokinetics, and pharmacodynamics. Formal guidelines for complex nonbiological drugs are less well developed, but many of the same issues apply. The situation is particularly difficult for MS DMTs due to the inability to perform pharmacokinetic studies for many of the DMTs, insensitivity of the clinical measures typically used in pivotal trials, and lack of validated nonimaging biomarkers that relate to efficacy.

Development of formal guidelines and approval of biosimilars has proceeded faster in Europe than in the United States. Since 2006, the European Medicines Agency (EMA) has approved 21 biosimilars (none for a MS DMT); approvals for 2, filgrastim and somatropin, subsequently were voluntarily withdrawn by the authorization holders. In the United States, the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) established the regulatory framework for the approval of small molecule generics through an Abbreviated New Drug Application (ANDA). The 2009 Biologics Price Competition and Innovation Act created an abbreviated approval pathway for biosimilars. The US Food and Drug Administration (FDA) has issued several draft guidances on biosimilar product development, though no final guidance. In 2015, generic filgrastim (Zarxio, Sandoz) became the first biosimilar approved in the United States.

Success in developing a generic drug depends on the ability to offer a similar, safe, and effective product at a cost saving. Too relaxed requirements may jeopardize efficacy or patient safety. Too stringent requirements create a disincentive to pharmaceutical companies. A key concept is that a generic is not required to be identical to the reference product but comparable or highly similar within a prespecified range, with no clinically meaningful differences in safety, purity, or potency. Thus, although a noninferiority study design has more statistical power, in situations where a clinical trial is required, an equivalence design is preferred to show that the generic alternative is neither less nor more effective than the reference product to a meaningful degree. In general, equivalence limits are 80%–125% for a particular parameter, but the sponsor and regulatory agencies negotiate the actual limits (figure 2).

MRI as the primary endpoint for pivotal trials of generic MS DMT

Approvals of the current DMTs for relapsing MS were based on demonstrated benefit on relapse rate and, for some medications, disability worsening. Because these measures are relatively insensitive, MS pivotal trials usually last 24–36 months and enroll several hundred participants or more to provide adequate statistical power. MRI measures of lesion activity, gadolinium-enhancing (Gd+) lesions and new or enlarged T2-hyperintense lesions, are more sensitive to

Figure 2 Potential results of trials seeking to demonstrate equivalence

^a The upper and lower equivalence limits are negotiated with regulatory agencies. ^{b,c} The point estimates and 95% confidence interval (CI) fall within the equivalence limits, representing a positive equivalence trial. ^d Although the point estimate is the same as in (b), the 95% CI is not within the equivalence limits, representing a negative equivalence trial. ^{e,f} The results represent negative equivalence trials. Gd+ = gadolinium-enhancing.

the ongoing inflammatory process, so these measures are routinely used as the primary endpoint in phase 2 studies. However, because these MRI outcomes correlate weakly with clinical features in individual patients, they are accepted by regulatory agencies only as supporting secondary endpoints in pivotal trials of new agents.

To evaluate whether MRI lesion activity could serve as a surrogate for relapses in MS trials, a meta-analysis of 23 clinical trials was performed demonstrating strong correlation between treatment effects on MRI lesion activity and clinical relapses at the trial level.³ A subsequent meta-analysis of 31 additional MS clinical trials confirmed the original findings and demonstrated that the magnitude of treatment effect on MRI lesion activity in the phase 2 trial predicted the magnitude of treatment effect on relapse rate in subsequent corresponding phase 3 trials.⁴ Thus, one setting in which MRI lesion activity might be an appropriate primary endpoint in a pivotal trial is the comparison of a generic and brand MS DMT with established effects on MRI lesion activity and relapses.

Glatiramer acetate (GA) to treat MS

GA is a complex mixture of polypeptides formed from the random polymerization of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine developed at the Weizmann Institute in the 1960s to study structural features of antigens involved in induction of the animal model of MS, experimental autoimmune encephalomyelitis (EAE).⁵ The mechanism of action of GA accounting for its clinical benefit in MS is incompletely understood but is hypothesized to involve competition with myelin autoantigens at the major histocompatibility complex class II binding site on antigen-presenting cells, induction of antigen-specific Th2 T cells leading to bystander suppression of inflammation, and stimulation of neurotrophic factor secretion by immune cells.⁵

Typically, the first marketed generic drug is only moderately reduced in price and enjoys 180-day market exclusivity.

Clinical trials demonstrated benefit of GA on relapse rate,^{6,7} MRI lesion activity,⁸ and rate of conversion to clinically definite MS in patients with clinically isolated syndrome,⁹ and demonstrated relapse rate reduction comparable to interferon- β .^{10–12} GA 20 mg administered by daily SC injection (Copaxone; Teva, Petah Tikva, Israel) was approved by the FDA to treat relapsing-remitting MS in 1996, and was approved in Europe in 2000 (France in 2003). It was approved to treat clinically isolated syndrome in the United States and Europe in 2009. More recently, a new 40-mg formulation administered by SC injection 3 times per week was shown to reduce relapses and MRI lesion activity vs placebo¹³ and was approved by the FDA in 2014. Despite the introduction of oral agents and monoclonal antibodies, as of 2014, GA was the most frequently prescribed MS DMT, based on its ease of use and extensive clinical experience supporting efficacy, safety, and generally good tolerability.¹⁴

Status of generic versions of GA

The patent for brand GA 20 mg daily ended in 2014. Following submission of an ANDA in December 2007, a generic GA (GLATOPA; Momenta/Sandoz, Cambridge, MA) was approved by the FDA in April 2015, based on demonstration of equivalent physicochemical characteristics plus immunologic and clinical effects in EAE.¹⁵ A clinical trial was not requested. Mylan/NATCO (Pittsburgh, PA) and Synthon/Pfizer (Nijmegen, the Netherlands) also filed ANDAs for generic GA products, in September 2009 and November 2011, respectively. In contrast, the EMA viewed GA as a complex nonbiological drug, and, analogous to a previous guideline on interferon- β ,¹⁶ advised Synthon to perform a clinical trial to confirm equivalent efficacy, safety, and tolerability in patients with MS, leading to the Glatiramer Acetate Clinical Trial to Assess Equivalence with Copaxone (GATE) trial.¹⁷ These events illustrate the differences in how the 2 regulatory agencies approached generic GA.

Results of the GATE trial

The GATE trial was a multicenter, randomized, double-blind, active- and placebo-controlled phase 3 trial. Key eligibility criteria included age 18–55 years, relapsing-remitting MS with ≥ 1 relapse in the prior year, and 1–15 Gd+ lesions on screening MRI. Eligible participants were randomized to generic GA (20 mg, Synthon, n = 353), brand GA (20 mg, n = 357), or placebo (n = 84) administered by daily SC injection for 9 months. Mean number of Gd+ lesions on monthly MRIs during months 7–9, the primary endpoint, was significantly reduced in the combined GA-treated group and in each GA group individually compared to the placebo group, confirming study sensitivity (i.e., GA was effective under the conditions of the study). The point estimate and 95% confidence interval of the ratio of estimated mean total number of Gd+ lesions during months 7–9 for generic vs brand GA was 1.095 (0.883–1.360), which was within the prespecified equivalence margins (0.727–1.375). Tolerability (including injection site reactions) and safety (incidence, spectrum, and severity of adverse events) were similar in the generic and brand GA groups. These results demonstrated that generic and brand GA have equivalent efficacy, tolerability, and safety over 9 months. Results of the 15-month extension were presented at the European Committee for Treatment and Research in Multiple Sclerosis 2015 meeting and showed similar efficacy, safety, and tolerability in participants treated with generic GA for 2 years and patients switched from brand GA.¹⁸

Take-home points

- A generic drug is not required to be identical to the reference product but comparable or highly similar within a prespecified range, with no clinically meaningful differences in safety, purity, and potency.
- Success in development of a generic drug depends on ability to offer a similar, safe, and effective product at a cost saving. Too relaxed requirements may jeopardize efficacy or patient safety. Too stringent requirements create a disincentive to pharmaceutical companies.
- The GATE trial provides a general template for equivalence trials of generic versions of anti-inflammatory MS DMTs.
- The effect generic versions of GA will have on overall medication costs depends on whether clinicians and patients are confident they are comparable to brand GA, how they are priced relative to brand GA and other approved DMTs, and whether patients accept daily dosing with the availability of a 3 times per week option.

The GATE trial is of interest for several reasons. It was the first pivotal trial of a generic MS DMT. It utilized an equivalence design rather than the superiority design more familiar to the MS field. Use of an equivalence design (rather than noninferiority), the prespecified equivalence margins, and inclusion of a small placebo to confirm study sensitivity were based on input from the EMA. GATE was the first MS pivotal trial to employ an MRI-related outcome as the primary endpoint, based on the meta-analyses described above.^{3,4} The specific primary endpoint, total number of Gd+ lesions during months 7–9, and estimated statistical power were based the European/Canadian Glatiramer Acetate Trial, which demonstrated that GA reduced Gd+ lesions on monthly MRI scans over 9 months compared to placebo and that the treatment effect developed over time, becoming significant after month 6.⁸ The GATE trial provides a general template for equivalence trials of generic anti-inflammatory MS DMTs.

DISCUSSION

The rising costs of prescription drugs are concerning for all health care stakeholders and various proposals to address this issue have been presented.^{19,20} Neurologists, in particular, are affected as the cost of MS DMTs are responsible for 64%–91% of the total cost of MS care.²¹ The introduction of generic drugs into the MS treatment landscape hopefully will reduce medication costs and, thus, the overall health care financial burden of MS. Whether this occurs will depend on several factors. First, clinicians and patients must be confident that the generic drugs have comparable efficacy, safety, and tolerability as the brand drug.

As discussed above, it is not straightforward to demonstrate this point for biological and complex nonbiological agents. The second factor is price. Typically, the first marketed generic drug is only moderately reduced in price and enjoys 180-day market exclusivity. After additional generic products reach the market, greater price reductions are seen, sometimes up to 85%.²² GLATOPA's wholesale market price at introduction was \$63,000, about 15% less than the cost of daily Copaxone, but only slightly less than the cost of Copaxone 40 mg 3 times per week. Patients who are taking the 3 times a week formulation may resist returning to daily injections despite potential cost savings. Other factors include tiering, required step therapy, and individual out-of-pocket costs of various prescription drug plans.²³ Neurologists have the responsibility to guide policymakers as they attempt to address rising medication costs by continuing to advocate for accessibility to DMTs based on objective evidence, value, and need to individualize care.²⁴

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L.H. Hua has served on scientific advisory boards for Genzyme and EMD Serono; has received funding for travel from Genzyme and speaker honoraria from Multiple Sclerosis Association of America; serves as a consultant for Gerson Lehrman Group; serves on speakers' bureaus for Teva and Genzyme; and receives research support paid to her institution from Novartis, Receptos, Biogen, and Roche. J.A. Cohen serves on scientific advisory boards/as a consultant for Genentech, Genzyme/Sanofi, Novartis, and Receptos; has received speaker honoraria from Teva; serves as Co-Editor of *Multiple Sclerosis Journal: Experimental, Translational and Clinical*; receives publishing royalties for *Multiple Sclerosis Therapeutics, 4th ed.* (Cambridge University Press, 2011); receives research support paid to his institution from Genzyme, Novartis, Receptos, Synthon, and Teva; and receives research support from the U.S. Department of Defense, NIH, National MS Society, and Consortium of MS Centers. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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