Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

In the special article "Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis," Rae-Grant et al. reported the findings of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology based on reviewing the evidence on starting, switching, and stopping disease-modifying therapies for clinically isolated syndrome, relapsing-remitting MS, and progressive forms of MS. In response, Dr. Tran, on behalf of Genentech, argues that the report did not make it clear that data on annualized relapse rate reduction and relative risk of in-study disability progression for ocrelizumab (presented along with other therapies in figures 1 and 3) were from direct comparisons with subcutaneous interferon-β-1a 44 μg 3 times weekly in 2 phase 3 randomized, double-blind, double-dummy trials. In response, Dr. Rae-Grant agrees that this information should have been included, but notes that statements in the text of the summary and in a key accompanying table acknowledged the superior efficacy of ocrelizumab compared with interferon- β-1a 3 times weekly. Dr. Rae-Grant also notes that data on subgroup analysis of treatment of highly active MS with ocrelizumab were not available at the time of publication of the systematic review.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
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Reader response: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Katherine R. Tran (San Francisco)
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Genentech recognizes that high-quality and trustworthy guidelines, such as those published by the American Academy of Neurology, are important both for providers to optimize patient care and for payers to manage appropriate utilization of multiple sclerosis (MS) treatments. We appreciate the opportunity to provide the following corrections to inform accurate recommendations for health care decision makers.

The Comprehensive Systematic Review Summary omits key information regarding ocrelizumab in figures 1 and 3.[1] Figure 1 lists disease-modifying therapies (DMTs) by annualized relapse rate (ARR) reductions from highest to lowest; figure 3 lists DMTs by relative risk of in-study disability progression at 2 years. The figures do not include a footnote indicating that the ARR and disability progression for ocrelizumab are relative to subcutaneous interferon-β-1a 44 μg 3 times weekly, although there is such a note included for alemtuzumab.

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The efficacy and safety of ocrelizumab compared with subcutaneous interferon-β-1a 44 μg 3 times weekly in RMS was evaluated in 2 identical, phase 3, randomized (1:1), double-blind, double-dummy, head-to-head comparative trials.[2,3] Readers may infer indirect treatment comparisons using these figures, and the omission of this fundamental detail misrepresents the relative efficacy of MS DMTs.

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 2018;90:789–800.
2. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221–234.
3. Genentech, Inc Highlights of prescribing information: ocrevus (ocrelizumab) injection, for intravenous use: full prescribing information. Available at: gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed: December 12, 2018.

Author response: Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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I thank Dr. Tran for the comment on our comprehensive systematic review summary for the American Academy of Neurology guideline on disease-modifying therapy for adults with multiple sclerosis (MS).[1]

In regard to figures 1 and 3,[1] Dr. Tran correctly points out that critical information related to the ocrelizumab findings should have been included in each figure to indicate that the ocrelizumab findings are in comparison with interferon-β-1a (IFN-β-1a). We regret missing this in our proofing of this set of long and complex articles.

The text of the summary, a key accompanying table, and the full-text guideline document reflect the active comparator using IFN-β-1a subcutaneous 3 times per week.[1] The following language was used for conclusions about ocrelizumab: "Ocrelizumab[13] is more effective than IFN-β-1a subcutaneous 3 times per week … (high confidence);" "Ocrelizumab[13] is more effective than IFN-β-1a 44 μg subcutaneous 3 times weekly… (high confidence)."

In addition, a key table of efficacy for reducing the annualized relapse rate for relapsing MS documented the active comparator status in the summary[1] as follows: "Ocrelizumab more effective than IFN-β-1a subcutaneous 3 times per wk."

This information should have been included in the published article, and we will notify the *Neurology* journal of this error as quickly as feasible.

We further appreciate your comments about subgroup analysis of treatment of highly active MS with ocrelizumab. Unfortunately, these data were not published when we completed our systematic review.

Medicine is a constantly evolving process; we noted this in our summary. How payers use guidelines to make decisions about access to care is beyond the scope and control of guideline development.

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90:789–800.

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Editors' note: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

In the article "High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy," Albrecht et al. investigated the prevalence of neutralizing antibodies (NAbs) against botulinum neurotoxin type A (BoNT/A) in a monocentric, observational cross-sectional study of 596 outpatients treated with BoNT/A over a mean of 5.3 years for different indications and found that 13.9% had measurable NAbs. The probability of developing NAbs increased with the single and cumulative dose of treatment and was associated with the BoNT/A formulation used, leading the authors to recommend avoiding booster injections and reducing the individual injected doses. In response, Dr. Jankovic notes that the authors did not mention other studies that showed a much lower frequency of NAbs, although after shorter periods of observation, and indicates that no data were provided regarding any correlation between the presence of NAbs and clinical response. In this regard, Dr. Jankovic notes that none of the patients in a previous study with blocking antibodies identified by the mouse protection assay (MPA) had any clinical response, suggesting that the MPA may be more clinically meaningful. In their reply, Albrecht et al. postulate that lower rates of NAbs in previous studies may relate to lower sensitivity of the MPA, lower BoNT doses used, and substantially shorter duration of treatment. In contrast to Dr. Jankovic's findings, they report that all their patients with NAbs opted to continue treatment and reported ongoing subjective benefit. Both the authors and Dr. Jankovic agree on the need for novel assays with higher sensitivity and specificity that are (ideally) not animal based. In another response, Mulroy et al. caution that the authors' conclusions may mislead readers into thinking that long-term treatment with frequent or repeated BoNT injections can result in clinical treatment failure. Like Dr. Jankovic, they too highlight the absence of data on clinical effectiveness in this study and note that NAb serostatus did not always correlate with clinical response in previous studies. They also seek to clarify the authors' disclosures, given that the study was funded by Merz Pharmaceuticals, which manufacturers one of the BoNT formulations studied. Replying to these comments, Albrecht et al. argue that there is consensus that the induction of NAbs should be avoided, as they are associated with reduced treatment response in several studies. They acknowledge that they do not have information about NAb induction with treatment intervals shorter than 10 weeks in their study, note the difficulty of comparing treatment efficacy across different indications, and concede that efficacy data were not available for all patients. They also state that pharmaceutical funding had no influence on the interpretation or analysis of their data. This correspondence highlights enduring uncertainty in the field regarding the clinical implications of NAbs as detected by existing animal-based assays.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
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Reader response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

Joseph Jankovic (Houston)
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In the article by Albrecht et al.,[1] the authors reported nearly 14% prevalence of neutralizing antibodies, determined by mouse hemidiaphragm assay (MHDA), among 596 patients treated with botulinum neurotoxin type A (BoNT/A), mostly with abo-BoNT/A (n = 324). They cited similar

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prevalence of neutralizing antibodies based on their own study,[2] but they failed to mention other studies showing much lower frequency of such antibodies, albeit after a shorter observation period. For example, in a prospective study of 326 patients with cervical dystonia treated with BoNT/A, only 1.2% tested positive for antibodies detected by the mouse protection assay (MPA).[3] Albrecht et al.[1] provided no data on the correlation between the presence of antibodies detected by MHDA and clinical response, although they stated that their patients were "still responding."

In contrast, none of our patients with positive titers for blocking antibodies tested by MPA had any clinical response, indicative of true immunoresistance.[4] Therefore, the latter assay is more clinically meaningful as it correlates well with clinical response, which may explain the differences in the reports of secondary unresponsiveness among various studies using different assays and BoNT products.[5] More sensitive and specific assays that are not animal based are needed to monitor the emergence of blocking antibodies, particularly in patients treated chronically with high doses of BoNT.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology 2019;92:e48–e54.
2. Hefter H, Rosenthal D, Moll M. High botulinum toxin-neutralizing antibody prevalence under long-term cervical dystonia treatment. Mov Disord Clin Pract 2016;3:500–506.
3. Brin MF, Comella CL, Jankovic J, et al. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord 2008;23:1353–1360.
4. Hanna PA, Jankovic J. Mouse bioassay versus Western blot assay for botulinum toxin antibodies: correlation with clinical response. Neurology 1998;50:1624–1629.
5. Bellows S, Jankovic J. Immunogenicity Associated with Botulinum Toxin Treatment. Toxins (Basel). 2019:Aug 26;11(9).

Author response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

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We thank Dr. Jankovic for his valuable comments on our article.[1] The study by Brin et al.,[2] which, along with similar studies, is analyzed in a review referenced in our article,[3] reported lower rates of neutralizing antibodies (NAbs) (1.4% at a mean treatment duration of 2.5 years and maximum duration of 4 years) in cervical dystonia. Reasons may be a lower sensitivity of the mouse protection assay (MPA) compared with our mouse hemidiaphragm test, the lower doses applied, and the fact that the treatment duration was substantially shorter than in our study (mean 5.3 years and maximum 23 years). We completely agree that the clinical relevance of the observed NAbs should be investigated by assessing the clinical response. These investigations are underway and will be the subject of a following publication. However, we can already state that we do not share Dr. Jankovic's impression that all patients with detectable NAbs display complete unresponsiveness. All our patients were on continued treatment by choice and reported at least some subjective benefit of therapy.[1] This is in line with previous studies using the MPA that also reported responsiveness in some patients despite positive NAbs.[2,4] We agree that novel, ideally not animal-based, assays with high sensitivity and specificity should be established and validated.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology 2019;92:e48–e54.

Author disclosures are available upon request (journal@neurology.org).

2. Brin MF, Comella CL, Jankovic J, et al. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord 2008;23:1353–1360.
3. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. J Neural Transm (Vienna) 2013;120: 275–290.
4. Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®) across multiple indications. Mov Disord 2010;25:2211–2218.

Reader response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

Eoin Mulroy (London), Bettina Balint (Heidelberg, Germany), and Amit Batla (Luton, UK)
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We read with interest the article by Albrecht et al.,[1] which demonstrated that 14% of 596 patients treated with various botulinum toxin (BoNT) preparations over 2–5 years developed neutralizing antibodies (Nabs). Although the study clearly focuses on the presence of Nabs and not on the clinical effect, the conclusions by Albrecht et al.[1] that "… avoiding booster injections and providing short intervals between injections… may diminish the risk of NAb induction…" and that "… the dose per injection session should be kept as low as possible to avoid clinically relevant immunization…" could mislead readers into believing that long-term treatment with frequent or repeated BoNT injections can result in clinical treatment failure.

The authors stated that "… patients were still responding (at least partially)…,"[1] but do not include data on clinical effectiveness. Most prior studies in this area have done so, as this greatly impacts on patient management.[2] It would be useful to know whether these data were not collected or have been omitted from publication intentionally. As previously demonstrated, Nab serostatus does not necessarily correlate with clinical response to repeated injections.[2,3]

Last, the authors reported no disclosures related to the study,[1] yet the study was funded by a pharmaceutical company that manufactures one of the BoNTs included in the study. This needs clarification.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology 2019;92:e48–e54.
2. Fabbri M, Leodori G, Fernandes RM, et al. Neutralizing antibody and botulinum toxin therapy: a systematic review and meta-analysis. Neurotox Res 2016;29:105–117.
3. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord 2008;23:1353–1360.

Author response: High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy

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We thank Mulroy et al. for their comment on our article.[1] The association of neutralizing antibodies (NABs) against botulinum neurotoxin A and a reduced treatment response has been reported in several publications.[2,3] It is, therefore, consensus that the induction of NABs should be avoided if possible. Given the constant treatment intervals >10 weeks in our study,[1] we do

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not have information about NAB induction with shorter treatment intervals. With these regimens, an impact was reported in previous studies.[4,5] Our investigation was directed to identify other factors relevant for the induction of NABs and the prevalence in a large sample of treatment responsive patients across different indications. As comparing treatment efficacy across different indications is challenging and efficacy data was not available for all patients, we chose to not focus on treatment response.

Funding by Merz Pharmaceuticals was transparently reported at the bottom of the manuscript and all unrelated disclosures are listed on the journal webpage. As this funding had no influence on the interpretation or analysis of the data, it was not additionally listed as a relevant disclosure.

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology 2019;92:e48–e54.
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4. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. J Neural Transm (Vienna) 2013;120:275–290.
5. Lange O, Bigalke H, Dengler R, et al. Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing? Clin Neuropharmacol 2009;32:213–218.

CORRECTION

Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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In the special article "Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," by Rae-Grant et al.,[1] there are errors in figures 1 and 3. In figure 1, a superscript "a" is missing from "Ocrelizumab" to indicate the comparator intervention (interferon-β-1a 44 μg 3 times per week subcutaneously); in figure 3, a superscript "b" is missing from "Ocrelizumab," also to indicate the comparator intervention (interferon-β-1a). Additionally, in the table "Efficacy of disease modifying therapies (DMTs) for reducing the annualized relapse rate (ARR) and risk of relapse at 2 years," there should not be an entry for "very low" confidence for azathioprine under "Reduction of the ARR." The entry for very low confidence for azathioprine under "Reduction of risk of relapse at 2 y" appears correctly. The authors regret the errors.

Reference

1. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90:789-800.

Author disclosures are available upon request (journal@neurology.org).

Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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