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Letter to the Editor

[Translated article] Clinical decision making on retreatment with monoclonal antibodies in chronic/episodic migraine

Toma de decisiones clínicas sobre el retratamiento con anticuerpos monoclonales en la migraña crónica/episódica

García-Lloret et al. reported that discontinuance of treatment with monoclonal antibodies that inhibit the calcitonin gene-related peptide (anti-CGRP) in patients with chronic/episodic migraine results in a worsening of symptoms. As a result, retreatment was necessary within 4 months after discontinuance.[1] The authors also report that 2/3 of the patients responded to retreatment with anti-CGRP.

"Therapeutic rest" or temporary treatment discontinuation is used in chronic diseases to reduce the risk for adverse events (AEs) and/or minimize treatment costs, as anti-CGRP antibodies have a significant cost. Moreover, in the case of previously treated chronic/episodic migraine, the therapeutic options after failure of anti-CGRP therapy are limited. Indeed, clinicians usually offer the use of an anti-CGRP antibody following failure of a previous treatment with another anti-CGRP antibody (the so-called "switching" approach). The switching strategy is based on low-quality scientific evidence and, according to some recommendations, the efficacy of this strategy has not been sufficiently demonstrated.[2] Temporary discontinuance of anti-CGRP can also be used to prolong the efficacy of this line of treatment before it is no longer effective. Therefore, studies about the efficacy of "therapeutic rest" are clearly warranted.

The main limitation of the study by García-Lloret et al. lies on the retrospective, single-arm design of the study. The absence of a comparator group (not receiving therapeutic rest), added to randomization, make it difficult to determine the cause-effect relationship between the study intervention and the results obtained.[3] The course of chronic diseases often involves fluctuations between acute episodes and disease control induced by either internal or environmental factors, thereby leading to the *regression toward the mean* phenomenon. When clinical symptoms exacerbate, the patients undergoing "therapeutic rest" could claim for retreatment with anti-CGRP therapy out of the belief that inadequate disease control is due to discontinuance rather than to disease fluctuations. Anti-CGRP retreatment could mask transition to disease control. However, patients not undergoing treatment discontinuance would associate the worsening of their symptoms to other factors and try to overcome the situation with support measures. This does not rule out a potential cause-effect relationship between temporary treatment discontinuation and the worsening of symptoms, but it only indicates that data should be interpreted with caution. The placebo effect and progressive loss of effectiveness over time, either with or without therapeutic rest, should also be considered.[4]

Developing a clinical trial is challenging, due to the limited resources available, the long time needed, the large sample of patients required and the lack of follow-up, which is often due to the limited personnel available for the high cost of drugs such as anti-CGRP antibodies. Therefore, it is necessary that predictive tools are developed for a reliable selection of candidates to temporary treatment discontinuance. These models are not exempt from some limitations, including the adjustment for some factors associated with treatment benefit without other unknown factors being evaluated. However, automatic machine learning models of patient and migraine characteristics, which could predict responses to anti-CGRP[5] antibodies, could be used as strategies to follow, adapting them to the reintroduction of these therapies.

Considering the aforementioned, it would be interesting to have information on the decisions made in your hospital after the study. Presuming that this approach would reduce costs and the risk for AEs, are you still using therapeutic rest despite the fact that a third of your patients *lost* response after retreatment because they associate this reduced efficacy to other factors? Or have you stopped using therapeutic rest due to the results obtained?

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Conflict of interest

The authors declare no conflicts of interest.

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