

Association between response to triptans and response to erenumab: real-life data

Ilaria Frattale

University of L'Aquila Department of Clinical Sciences and Applied Biotechnology: Università degli Studi dell'Aquila Dipartimento di Scienze Cliniche Applicate e Biotecnologiche

Valeria Caponnetto

University of L'Aquila Department of Clinical Sciences and Applied Biotechnology: Università degli Studi dell'Aquila Dipartimento di Scienze Cliniche Applicate e Biotecnologiche

Alfonsina Casalena

Ospedale Mazzini, Teramo

Maurizio Assetta

Ospedale Mazzini, Teramo

Maurizio Maddestra

'F. Renzetti' Hospital, Lanciano

Fabio Marzoli

'F. Renzetti' Hospital, Lanciano

Giannapia Affaitati

Gabriele d'Annunzio University of Chieti and Pescara: Università degli Studi Gabriele d'Annunzio Chieti Pescara

Maria Adele Giamberardino

Gabriele d'Annunzio University of Chieti and Pescara: Università degli Studi Gabriele d'Annunzio Chieti Pescara

Stefano Viola

'S. Pio da Pietrelcina' Hospital, Vasto

Amleto Gabriele

'SS. Annunziata' Hospital, Sulmona

Francesca Pistoia

University of L'Aquila Department of Clinical Sciences and Applied Biotechnology: Università degli Studi dell'Aquila Dipartimento di Scienze Cliniche Applicate e Biotecnologiche

Davide Cerone

San Salvatore Hospital: Ospedale Civile San Salvatore, L'Aquila

Carmine Marini

University of L'Aquila Department of Clinical Medicine Life Health and Environmental Sciences: Università degli Studi dell'Aquila Dipartimento di Medicina Clinica Sanita Pubblica Scienze della Vita e dell'Ambiente

Simona Sacco (✉ simona.sacco@univaq.it)

University of L'Aquila <https://orcid.org/0000-0003-0651-1939>

Raffaele Ornello

University of L'Aquila Department of Clinical Sciences and Applied Biotechnology: Università degli Studi dell'Aquila Dipartimento di Scienze Cliniche Applicate e Biotecnologiche

Short report

Keywords: triptans, erenumab, migraine treatment, CGRP

Posted Date: November 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-100067/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 6th, 2021. See the published version at <https://doi.org/10.1186/s10194-020-01213-3>.

Abstract

Background. Triptans and erenumab are both migraine-specific agents acting on the calcitonin gene-related peptide pathway. Therefore, response to triptans might be associated with response to erenumab.

Main body. In our study, consecutive patients referring to the Headache Centers of the Abruzzo region from January 2019 to March 2020 and treated with erenumab were interviewed about past use and efficacy of triptans. Triptan users were classified as 'triptan responders' if they were headache-free 2 hours after treating ≥ 3 migraine attacks with ≥ 1 triptan. We considered patients as 'erenumab responders', if they had a $\geq 50\%$ mean reduction in monthly migraine days between the 4th and the 6th month from treatment start compared with baseline. Of 91 triptan users, 73 (80.2%) were triptan responders and 58 (63.7%) were erenumab responders. The odds ratio of being erenumab responder was 3.64 (95% CI, 1.25-10.64) for triptan users as compared to non-users. ($P=0.014$). Besides, starting erenumab improved triptan response in both erenumab responders and non-responders.

Conclusions. Our data of an association between response to triptans and response to erenumab can be useful for patient advice and to improve the understanding of migraine pathophysiology and treatment.

Background

Migraine affects 14.4% of adults worldwide [1]. Despite the high burden of migraine, preventive treatments were not disease-specific until the advent of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway [2, 3]. While the development of migraine-specific preventive treatments is recent, acute treatments that are specific for migraine are available since the 1990s. Triptans are agonists of the 5-hydroxytryptamine (5-HT) receptors 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} having exerting their antimigraine effects by constricting extracerebral blood vessels, reducing trigeminal sensory nerve activation, and thus inhibiting vasoactive peptide release including substance P and CGRP [4]. Therefore, triptans indirectly share their target with onabotulinumtoxin A and monoclonal antibodies targeting the CGRP pathway [5]. Hence, it can be speculated that migraineurs whose attacks respond to triptans might also have a favorable response to the new migraine-specific preventive treatments. In the present real-life study, we assessed 1) whether previous response to triptans predicts the subsequent efficacy of erenumab; 2) whether the loss of efficacy – wear-off – of triptans over time predicts erenumab ineffectiveness, and 3) whether erenumab treatment improves the efficacy of triptans.

Methods

This is an ancillary study from a real-life observational study on patients treated with erenumab [6]. The study was approved by the Internal Review Board of the University of L'Aquila with protocol number 44/2019; each patient signed an informed consent. The study database is available from the Corresponding Author upon reasonable request.

Our study included patients aged 18 to 65 consecutively treated with erenumab from January 2019 to March 2020 in the Headache Centers of Avezzano, L'Aquila, Sulmona, Teramo, Chieti, Lanciano, and Vasto. All patients had a diagnosis of migraine with or without aura according with International Classification of Headache Disorders (ICHD) criteria [7]. For each patient we recorded sex, age, and migraine characteristics.

We collected information on the use of triptans by means of a structured questionnaire administered via telephone interview. Patients were asked about past use of the six triptans available in Italy, namely almotriptan, eletriptan, frovatriptan, rizatriptan, sumatriptan, and zolmitriptan, at any time before starting erenumab treatment. Information was checked with medical chart review where available.

Patients who reported use of at least one triptan for at least three migraine attacks were considered triptan users. Triptan users were classified as 'triptan responders' if they were headache-free within 2 hours after treating at least three migraine attacks with one triptan [8]; the remaining patients were classified as 'triptan non-responders'. Triptan responders were also asked about a decreased response to triptans over time, configuring the 'wear-off' phenomenon. Those same patients were also asked whether the efficacy of triptans improved after starting treatment with erenumab.

Regarding erenumab treatment, patients were classified as 'erenumab responders' if reporting a mean \geq 50% reduction in monthly migraine days from baseline to month 4–6 of treatment, in accordance with a secondary end-point of the STRIVE trial [9]; the remaining patients were classified as 'erenumab non-responders'.

Statistical analysis

We reported descriptive statistics by using numbers and proportions or means and standard deviations (SDs) as appropriate. We reported the odds ratios (ORs) and 95% confidence intervals (CIs) of the association between triptan response and erenumab response by means of the chi squared statistics. According to the calculations made with G*Power software [10], we estimated that performing a chi squared analysis with a total sample size of $n = 88$ would be sufficient to detect a medium ($f = 0.3$) effect size between two groups with a P value < 0.05 and 80% power. We used Microsoft Excel and SPSS version 20 to perform the analyses.

Results

During the study period, 140 patients were treated with erenumab for at least 6 months; 105 of them (75.0%) answered to the questionnaire and 91 (86.6%) of them were included in the study because they resulted to be triptan users. Regarding erenumab, 58 (63.7%) of the included patients were erenumab responders and 33 (32.3%) were erenumab non responders; regarding triptans, 73 (80.2%) were triptan responders and 18 (19.8%) triptan non-responders. There were no major differences in baseline characteristics between erenumab responders and non-responders (Table 1); the only significant difference regarded triptan use. In fact, among erenumab responders, 51 (87.9%) were triptan responders

while among erenumab non-reponders, 22 (66.7%) were triptan responders. The OR of being erenumab responder was 3.64 (95% CI, 1.25–10.64) for triptan responders as compared to non-responders (P = 0.014; Fig. 2-A).

Table 1
Comparisons between erenumab responders and non-responders in the 91 triptan users

	Erenumab responders (n = 58)	Erenumab non-responders (n = 33)	P value
<i>N, %</i>			
Female	49 (84.5)	30 (90.9)	0.384
Chronic Migraine	53 (91.4)	29 (87.9)	0.591
Medication overuse	38 (65.5)	23 (69.7)	0.683
Aura	21 (36.2)	10 (30.3)	0.568
Allodynia	33 (56.9)	15 (45.5)	0.293
Preventive treatment failures			0.464
2–4	36 (62.1)	23 (69.7)	
>4	22 (37.9)	10 (30.3)	
Triptan responders	51 (87.9)	22 (66.7)	0.014
<i>Mean ± SD</i>			
Age	46.6 ± 9.5	46.6 ± 10.9	0.926
Migraine duration, years	25.0 ± 11.2	29.3 ± 12.3	0.143
Monthly headache days	21.8 ± 7.9	18.3 ± 9.4	0.084
Monthly medication days	18.2 ± 8.7	18.6 ± 8.2	0.833
Mean headache intensity	7.8 ± 1.8	7.7 ± 1.7	0.792

Forty-six triptan users (50.5%) reported triptan wear-off. Among erenumab responders, 28 (48.3%) had triptan wear-off, while among erenumab non-responders 18 (54.5%) had triptan wear-off. The OR of being erenumab responder was 0.78 (95% CI, 0.33–1.83) for patients reporting triptan wear-off as compared to those not reporting triptan wear-off (P = 0.565; Fig. 2-A).

After starting erenumab treatment, 52 patients (57.1%) had further use of triptans; 29 (55.8%) of them reported an improvement in triptan effectiveness; 19 (52.8%) erenumab responders and 10 (62.5%)

erenumab non-responders reported an improvement in triptan effectiveness. The proportion of patients reporting an improvement in triptan effectiveness was similar in erenumab responders and erenumab non-responders (52.8% vs 62.5%; OR 0.67; 95% CI, 0.20–2.24; P = 0.265; Fig. 2-B).

Discussion

In our study, patients showing a favorable response at any time to at least one triptan had a higher probability to be responders to erenumab compared with those not responding to triptans. This information is important as it may improve our understanding of migraine pathophysiology and treatment; it could also be used in clinical practice to advise patients about their chances of response to erenumab treatment. However, previous response to triptans alone should not represent a strict criterion to select patients for erenumab treatment, because many triptan non-responders were erenumab responders.

To our knowledge, this is the first study primarily addressing the association between the response to triptans and that to monoclonal antibodies targeting the CGRP pathway. A previous real-life study found a trend toward better response to erenumab in triptan responders compared with non-responders [11], being however underpowered to draw definite conclusions. The remaining available real-life studies on the safety and efficacy of erenumab [12–17] did not assess triptan response. Our finding is in line with a previous report which found an association between response to triptans and response to onabotulinumtoxin A [18]; however, the association found by this early study was not confirmed in a further study [19].

The findings of our study can be explained considering what we know about migraine pathophysiology. A common action on the trigeminovascular system [5] might explain the association between response to triptans and response to erenumab. A previous study found that patients responding to rizatriptan had higher jugular blood levels of CGRP during migraine episodes compared with patients not responding to rizatriptan; besides, patients responding to rizatriptan had a steep decrease in CGRP after the administration of rizatriptan, which was not found in non-responders [8]. In triptan non-responders, pain neurotransmitters different from CGRP might be important in the generation of migraine; thus, triptan non-responders might be less responsive to CGRP-targeted treatments. It is important to note that while erenumab was designed as a CGRP receptor blocker, the action of triptans on CGRP is indirect.

Data about the improvement in response to acute medication are not reported by randomized clinical trials, despite being relevant in clinical practice as an additional efficacy outcome of migraine preventive medication. Improving responsiveness to acute medication is a goal of migraine prevention [20] and might be an additional parameter to test the efficacy of preventative drugs. In our study, after starting erenumab, more than half of patients reported an improvement in their response to triptans. This favorable effect was appreciated not only in erenumab responders but also in erenumab non-responders; on the contrary, among patients treated with onabotulinumtoxin A only responders reported an improved response to triptans [19]. The improved response to triptans found in patients treated with erenumab can

be explained by synergy, as erenumab blocks the CGRP receptor, while the target of triptans is not the CGRP receptor itself. We cannot exclude that the improved response to triptans might also be explained by an overall improved response to acute medication, including triptans and non-steroidal anti-inflammatory drugs, in patients treated with a migraine preventative.

Our data are preliminary and should be taken with caution, as they come from a real-life, non-randomized study. Our study is also limited by a small sample size, allowing reliable univariate comparisons but not multivariate adjustments. Despite the high rate of response to the questionnaire (75%), ensuring the reliability of our sample, the retrospective recall of information through telephone interview is prone to recall bias. Moreover, due to the limited number of patients we could not address differences according to the different triptans. Lastly, our data only refer to patients treated with erenumab, a CGRP receptor antagonist, and are therefore not generalizable to monoclonal antibodies targeting the CGRP molecule.

Conclusion

According to our real-life data, patients reporting response to at least one triptan have a higher likelihood to respond to erenumab treatment compared with triptan non-responders. This information is relevant to improve our understanding of migraine and its treatments and to predict the efficacy of migraine-specific preventatives.

Abbreviations

5-HT
5-hydroxytryptamine
CGRP
calcitonin gene-related peptide
ICHD
International Classification of Headache Disorders
STRIVE
Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention

Declarations

Ethics approval and consent to participate

the study was approved by the Internal Review Board of the University of L'Aquila (Italy) and patients gave written informed consent according to the Declaration of Helsinki.

Consent for publication

not applicable.

Availability of data and materials

anonymized data operated or analyzed during this study are available from the Authors upon reasonable request.

Competing interests

RO declares financial and non-financial relationships with Eli Lilly and Novartis, non-financial relationships with Allergan, and Teva; SS had a financial relationship (lecturer or member of advisory board) with Abbott, Allergan, Novartis, Teva, and Eli Lilly; GA has received funds for congress participation from Innovet Italia Srl, Epitech Group and Lusofarmaco; MAG received funds for congress participation from IBSA; AC, IF, AG, MA, MM, FM, SV, DC, CM, and FP declare no competing interests.

Funding

the publication fee for the present paper was unconditionally granted by Novartis Farma S.r.l.

Authors' contributions

IF drafted the initial manuscript and revised it for intellectual content. SS and RO conceived the study, collected clinical data, and revised the manuscript. All the remaining Authors collected the data and revised the manuscript for intellectual content.

Acknowledgments

The Authors thank the study patients for their kind cooperation.

References

1. Global Burden of Disease 2016 Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17 11:954-76; doi: 10.1016/S1474-4422(18)30322-3.
2. De Matteis E, Guglielmetti M, Ornello R, Spuntarelli V, Martelletti P, Sacco S. Targeting CGRP for migraine treatment: mechanisms, antibodies, small molecules, perspectives. *Expert Rev Neurother.* 2020;1-15; doi: 10.1080/14737175.2020.1772758.
3. Tiseo C, Ornello R, Pistoia F, Sacco S. How to integrate monoclonal antibodies targeting the calcitonin gene-related peptide or its receptor in daily clinical practice. *J Headache Pain.* 2019;20 1:49; doi: 10.1186/s10194-019-1000-5.
4. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol.* 1993;33 1:48-56; doi: 10.1002/ana.410330109.

5. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system-40 years and counting. *Lancet Neurol.* 2019;18 8:795-804; doi: 10.1016/S1474-4422(19)30185-1.
6. Ornello R, Casalena A, Frattale I, Gabriele A, Affaitati G, Giamberardino MA, et al. Real-life data on the efficacy and safety of erenumab in the Abruzzo region, central Italy. *J Headache Pain.* 2020;21 32. doi: 10.1186/s10194-020-01102-9.
7. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018;38 1:1-211; doi: 10.1177/0333102417738202.
8. Sarchielli P, Pini LA, Zanchin G, Alberti A, Maggioni F, Rossi C, et al. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. *Cephalalgia.* 2006;26 3:257-65; doi: 10.1111/j.1468-2982.2005.01016.x.
9. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. *N Engl J Med.* 2017;377 22:2123-32; doi: 10.1056/NEJMoa1705848.
10. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39 2:175-91; doi: 10.3758/bf03193146.
11. Barbanti P, Aurilia C, Egeo G, Fofi L. Erenumab: from scientific evidence to clinical practice-the first Italian real-life data. *Neurol Sci.* 2019;40 Suppl 1:177-9; doi: 10.1007/s10072-019-03839-x.
12. Lambru G, Hill B, Murphy M, Tylova I, Andreou AP. A prospective real-world analysis of erenumab in refractory chronic migraine. *J Headache Pain.* 2020;21 1:61; doi: 10.1186/s10194-020-01127-0.
13. Russo A, Silvestro M, Scotto di Clemente F, Trojsi F, Bisecco A, Bonavita S, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. *J Headache Pain.* 2020;21 1:69; doi: 10.1186/s10194-020-01143-0.
14. Raffaelli B, Kalantzis R, Mecklenburg J, Overeem LH, Neeb L, Gendolla A, et al. Erenumab in Chronic Migraine Patients Who Previously Failed Five First-Line Oral Prophylactics and OnabotulinumtoxinA: A Dual-Center Retrospective Observational Study. *Front Neurol.* 2020;11:417; doi: 10.3389/fneur.2020.00417.
15. Kanaan S, Hettie G, Loder E, Burch R. Real-world effectiveness and tolerability of erenumab: A retrospective cohort study. *Cephalalgia.* 2020:333102420946725; doi: 10.1177/0333102420946725.
16. Matteo E, Favoni V, Pascazio A, Pensato U, Benini M, Asioli GM, et al. Erenumab in 159 high frequency and chronic migraine patients: real-life results from the Bologna Headache Center. *Neurol Sci.* 2020; doi: 10.1007/s10072-020-04667-0.
17. Cheng S, Jenkins B, Limberg N, Hutton E. Erenumab in Chronic Migraine: An Australian Experience. *Headache.* 2020; doi: 10.1111/head.13968.

18. Lovati C, Giani L, Mariotti D, Alessandro C, Tabae Damavandi P, Mariani C, Pantoni L. May migraine attack response to triptans be a predictor of the efficacy of Onabotulinum toxin-A prophylaxis? *Neurol Sci.* 2018;39 Suppl 1:153-4; doi: 10.1007/s10072-018-3388-0.
19. Eren OE, Gaul C, Peikert A, Gendolla A, Ruscheweyh R, Straube A. Triptan efficacy does not predict onabotulinumtoxinA efficacy but improves with onabotulinumtoxinA response in chronic migraine patients. *Sci Rep.* 2020;10 1:11382; doi: 10.1038/s41598-020-68149-1.
20. Sacco S, Bendtsen L, Ashina M, Reuter U, Terwindt G, Mitsikostas DD, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain.* 2019;20 1:6; doi: 10.1186/s10194-018-0955-y.

Figures

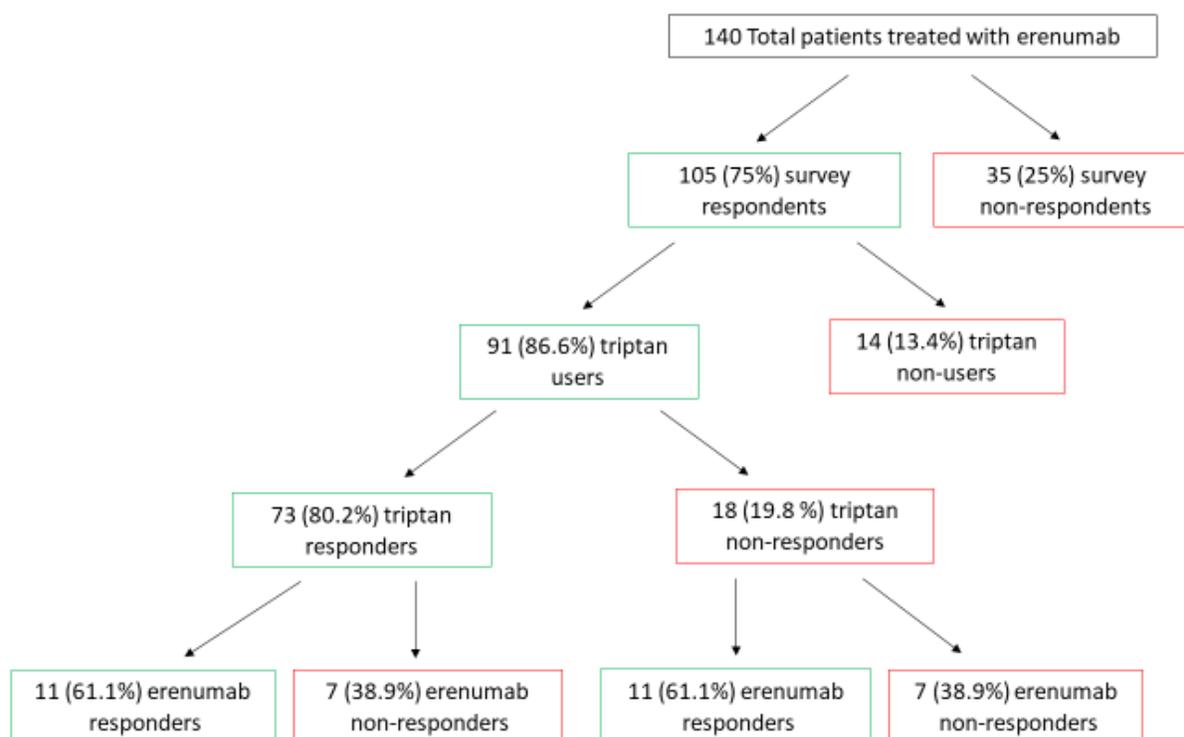


Figure 1

Flowchart of patient inclusion.

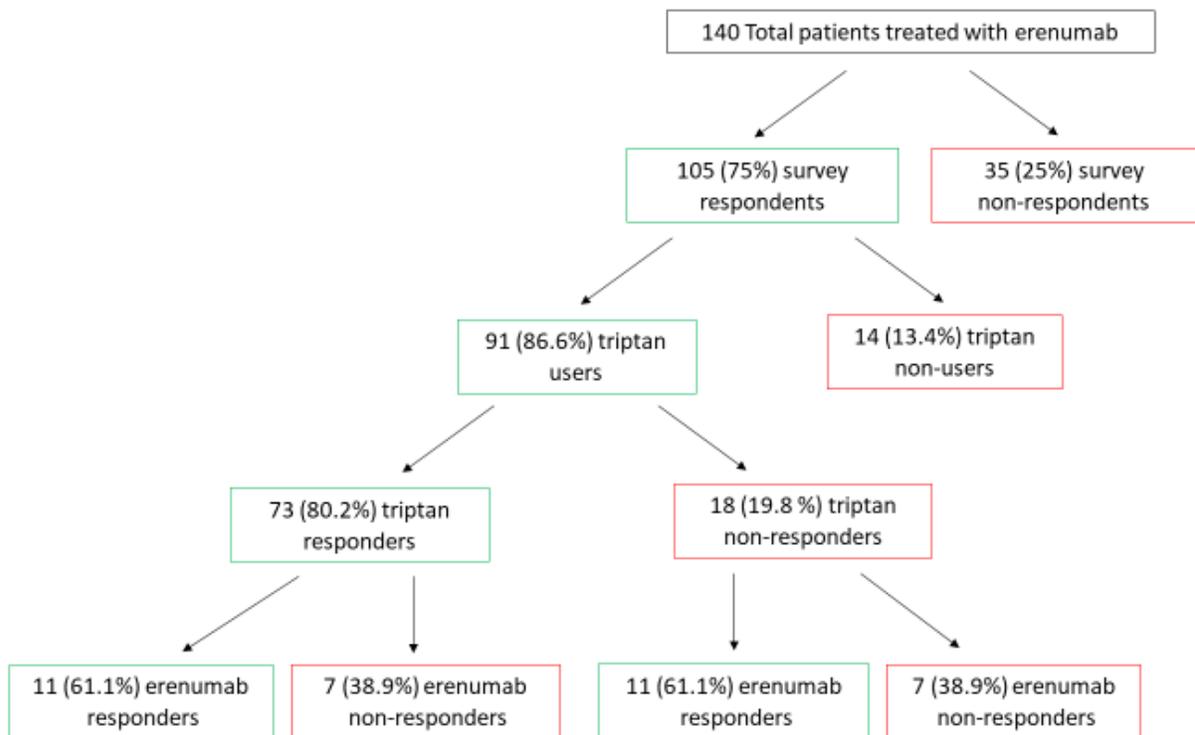


Figure 1

Flowchart of patient inclusion.

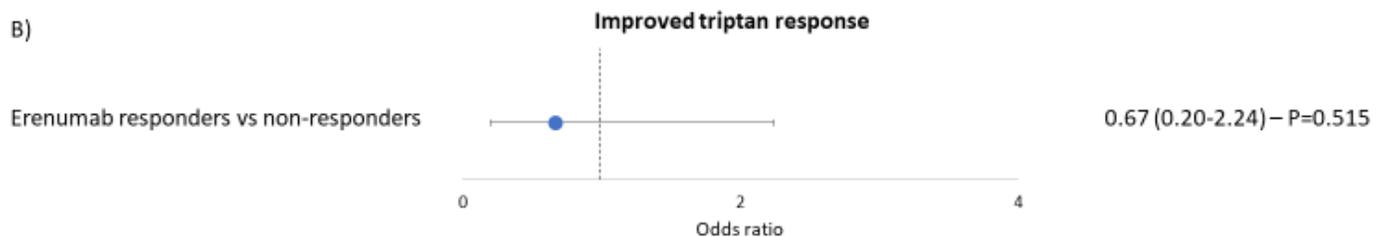
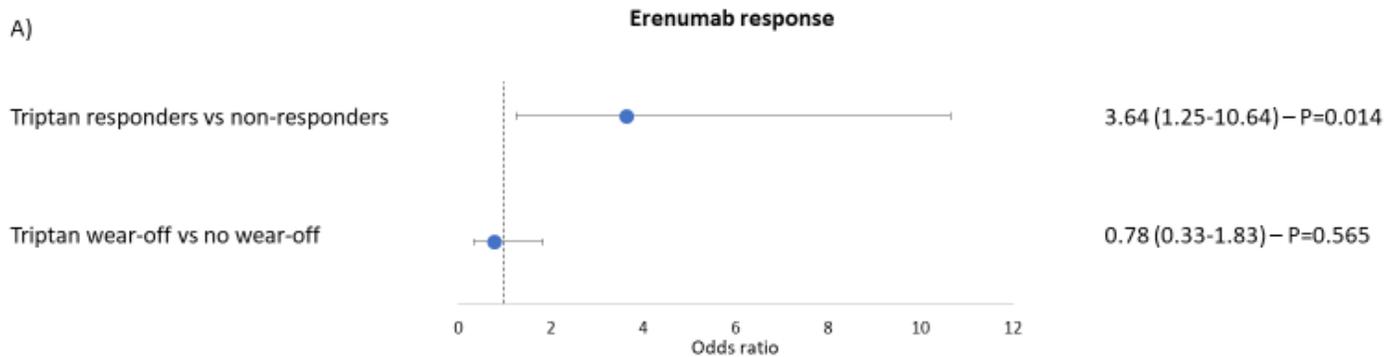


Figure 2

A) Odds ratios and 95% confidence intervals of erenumab response according to triptan response and triptan wear-off. B) Odds ratios and 95% confidence intervals of improvement in triptan response according to erenumab response.

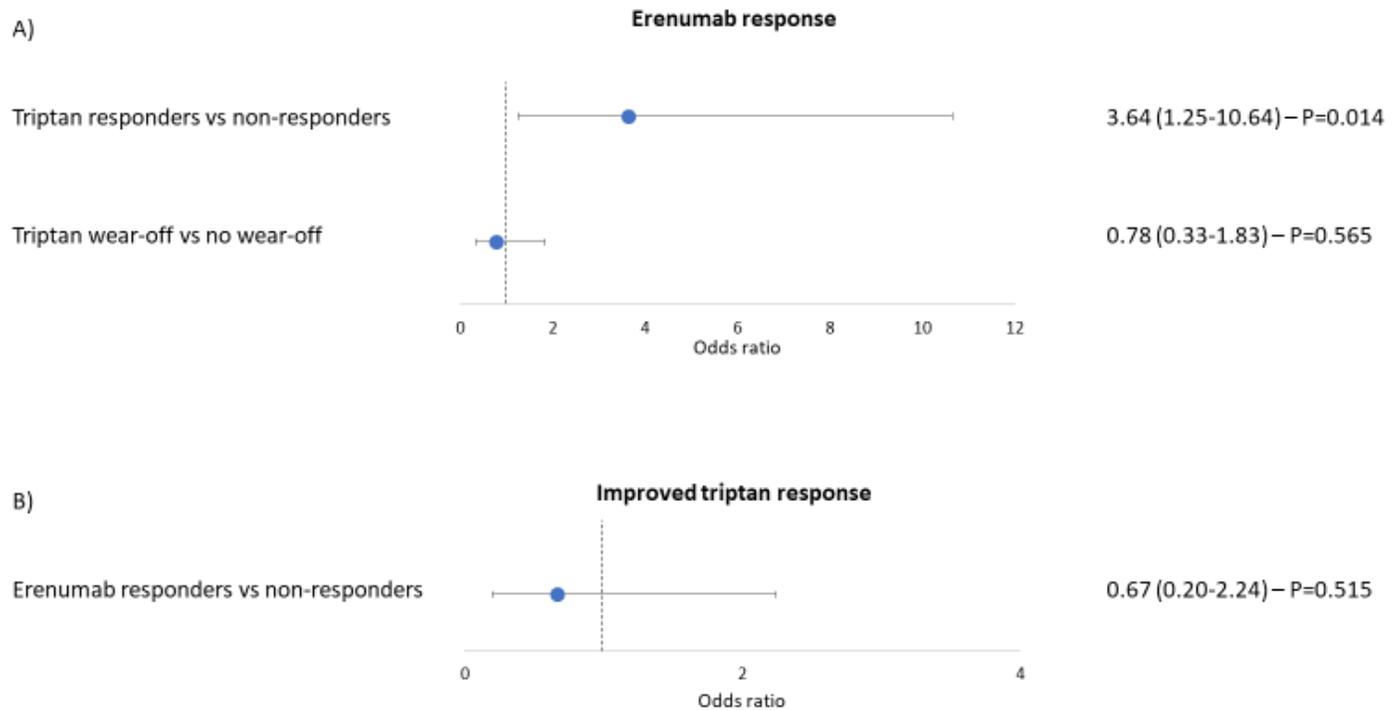


Figure 2

A) Odds ratios and 95% confidence intervals of erenumab response according to triptan response and triptan wear-off. B) Odds ratios and 95% confidence intervals of improvement in triptan response according to erenumab response.