Gastroenterol Hepatol. 2019;42(7):461–463

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

SPECIAL ARTICLE

Warnings on the safety of quinolones: Should *Helicobacter pylori* treatment prescriptions be modified?☆

Alertas sobre la seguridad de las quinolonas: ¿debemos modificar su prescripción en el tratamiento de la infección por *Helicobacter pylori*

Adrian G. McNicholl[a,b], **Javier P. Gisbert**[a,b,c,*]

[a] *Servicio de Aparato Digestivo, Hospital Universitario de La Princesa e Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain*
[c] *Universidad Autónoma de Madrid (UAM), Madrid, Spain*

Received 22 February 2019; accepted 2 March 2019
Available online 23 July 2019

In 2018, the United States Food and Drug Administration (FDA)[1] and the European Medicines Agency (EMA)[2] issued new warnings about serious adverse effects of fluoroquinolones. Both the FDA and the EMA demanded a change in the labelling of the entire class of antibiotics highlighting these new risks. They also discouraged the use of fluoroquinolones for most mild and moderate infections or where there is a therapeutic alternative, restricting their use exclusively to serious infections such as pneumonia, anthrax and plague, or other non-self-limiting infections in which the therapeutic benefit outweighs the risks.

The European Pharmacovigilance Risk Assessment Committee (PRAC) recently assessed the impact that potentially irreversible, long-lasting, disabling adverse reactions affecting the nervous and musculoskeletal systems might have on the benefit/risk ratio for this drug group. Accordingly, the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) [Spanish Agency of Medicines and Medical Devices] issued an informative note in October 2018 with a number of recommendations, including: (1) not to prescribe quinolone or fluoroquinolone antibiotics for the treatment of mild or self-limiting infections and (2) using quinolones or fluoroquinolones for the treatment of mild or moderately severe infections only when other recommended antibiotics are not effective or are not tolerated.[3]

It has been suggested that this warning could, at least partially, be in conflict with various therapeutic options currently recommended as rescue treatment after the failure of one or more drugs for the eradication of *Helicobacter pylori*.[4–6] In the specific case of Spain, these recommendations were recently issued by the ''4th Consensus Conference on the management of *Helicobacter pylori* infection'', in which rescue treatment with levofloxacin (along with bismuth quadruple therapy) was included as one of the two rescue options of choice.[4]

☆ Please cite this article as: McNicholl AG, Gisbert JP. Alertas sobre la seguridad de las quinolonas: ¿debemos modificar su prescripción en el tratamiento de la infección por *Helicobacter pylori*. Gastroenterol Hepatol. 2019;42:461–463.

* Corresponding author.
E-mail address: javier.p.gisbert@gmail.com (J.P. Gisbert).

Obviously, we are fully on board with the health authority recommendation for responsible use of antibiotics and the need to carefully analyse the available therapeutic options and their risk/benefit ratio before prescribing any drug. However, we feel it is important to remember that *H. pylori* causes a chronic infection that can trigger serious conditions such as peptic ulcer (possibly with complications, such as gastrointestinal bleeding) and gastric cancer, and that treatment requires the combined use of several antibiotics. Combined with other antibiotics, quinolones play an important role in the treatment of *H. pylori* infection, although it has to be said that current recommendations restrict their use exclusively as rescue after the failure of other antibiotic combinations.

Following the current recommendations of the aforementioned Spanish Consensus Conference,[4] the first-line treatments have effective rates of 90% or above. This would therefore limit the use of fluoroquinolones to less than 10% of patients, particularly in view of the fact that there are other recommended rescue treatments, such as the quadruple therapy with proton pump inhibitor, bismuth salts, tetracycline and metronidazole. We must not forget that these refractory patients tend to have multiple resistance to the previously used antibiotics, especially clarithromycin and metronidazole, which considerably reduces the therapeutic alternatives.[7] Therefore, taking into account the virtual lack of treatment options and the risks deriving from *H. pylori* infection, the question is whether the frequency, and in particular the severity, of the adverse effects of quinolones would still lead to their use as a rescue treatment being advised against.

Fortunately, some of the largest studies in the world to have assessed quinolones in the treatment of *H. pylori* infection have been carried out in Spain. In 2013, a Spanish multicentre study was published which had involved 17 hospitals and 1000 patients treated with a proton pump inhibitor, levofloxacin (500 mg/12 h) and amoxicillin for 10 days, and the rate of adverse effects was 20%; although 2.4% of these were classified as high intensity, none were serious.[8] In 2015, a new Spanish series, also multi-centre (250 patients), was published, replacing levofloxacin with moxifloxacin and lengthening therapy to 14 days; although the incidence of adverse effects was relatively high (25%, 7.6% of high intensity), no serious side effects were reported.[9] Also published in 2015 was another Spanish multicentre study which, on this occasion, assessed the addition of bismuth to traditional triple therapy with levofloxacin, extending the duration to 14 days and decreasing the daily dose of levofloxacin to 500 mg once a day.[10] Adverse effects were common (47%), but none were serious. Last of all, a recent meta-analysis which assessed the efficacy and safety of rescue treatment for *H. pylori* with quinolones did not identify serious adverse effects in the studies it included.[11]

The European Registry on the management of *H. pylori* infection (Hp-EuReg), an ambitious project led from Spain involving almost 300 hospitals in 27 countries in Europe and in which the efficacy and safety of more than 35,000 eradicating treatments have been registered, is a magnificent source of information on the use, efficacy and safety of antibiotics used in the eradication of *H. pylori*.[12] The data from this registry were presented recently at several European congresses and currently include a total of 3589 treatments with quinolones: the incidence of adverse effects was 25%, only 0.4% of which were considered serious (including mainly diarrhoea with associated time off work and vaginal candidiasis).

To sum up, in view of the results obtained in clinical practice, we believe that, for the time being, the recommendations issued by the ''4th Spanish Consensus Conference on *Helicobacter pylori* infection treatment'',[4] and by other international consensus groups,[5,6] regarding the use of fluoroquinolones as rescue treatment after eradication failure should not be modified. Having said that, we again insist on the need not only for responsible use of all antibiotics, and quinolones in particular, but also to notify all suspected adverse reactions and to remain alert to possible communications from national and international health authorities about serious adverse effects of these drugs.

Conflicts of interest

Dr Gisbert has acted as lecturer or advisor, or has received research funds, from MSD, AbbVie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Roche, Sandoz, Celgene, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Vifor Pharma, Almirall, Nycomed, AstraZeneca, Casen Recordati, Mayoly and Allergan.

Dr McNicholl has received payment for training activities from Allergan, MSD, Takeda and Nycomed, has been a lecturer for Allergan and Mayoly Spindler, and advisor to Mayoly Spindler.

References

1. FDA. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. Safety Announcement: Food and Drug Administration; 2018, 07-10-2018.
2. EMA. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics: European Medicines Agency; 2018, 16/11/2018.
3. AEMPS, 2018. Available from: https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2018/docs/NI_MUH_FV-14-2018-quinolonas-fluoroquinolonas.pdf
4. Gisbert JP, Molina-Infante J, Amador J, Bermejo F, Bujanda L, Calvet X, et al. IV Spanish consensus conference on *Helicobacter pylori* infection treatment. Gastroenterol Hepatol. 2016;39:697–721.
5. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection — the Maastricht V/Florence Consensus Report. Gut. 2017;66:6–30.
6. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto Consensus for the treatment of *Helicobacter pylori* infection in adults. Gastroenterology. 2016;151:51–69.e14.
7. Kobayashi I, Saika T, Muraoka H, Murakami K, Fujioka T. *Helicobacter pylori* isolated from patients who later failed *H. pylori* eradication triple therapy readily develop resistance to clarithromycin. J Med Microbiol. 2006;55:737–40.
8. Gisbert JP, Perez-Aisa A, Bermejo F, Castro-Fernandez M, Almela P, Barrio J, et al. Second-line therapy with levofloxacin after failure of treatment to eradicate *Helicobacter pylori* infection:

time trends in a Spanish Multicenter Study of 1000 patients. J Clin Gastroenterol. 2013;47:130–5.
9. Gisbert JP, Romano M, Molina-Infante J, Lucendo AJ, Medina E, Modolell I, et al. Two-week, high-dose proton pump inhibitor, moxifloxacin triple *Helicobacter pylori* therapy after failure of standard triple or non-bismuth quadruple treatments. Dig Liver Dis. 2015;47:108–13.
10. Gisbert JP, Romano M, Gravina AG, Solis-Munoz P, Bermejo F, Molina-Infante J, et al. *Helicobacter pylori* second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. Aliment Pharmacol Ther. 2015;41:768–75.
11. Marin AC, Nyssen OP, McNicholl AG, Gisbert JP. Efficacy and safety of quinolone-containing rescue therapies after the failure of non-bismuth quadruple treatments for *Helicobacter pylori* eradication: systematic review and meta-analysis. Drugs. 2017;77:765–76.
12. McNicholl A, Nyssen O, Bordin D, Tepes B, Perez-Aisa A, Vaira D, et al. Pan-European Registry on *H. pylori* management (Hp-EuReg): first-line treatment use and efficacy trends from 2013 to 2018. Helicobacter. 2018;23 Suppl 1:11.