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REVIEW

Newer agents for *Helicobacter pylori* eradication

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Abstract: *Helicobacter pylori* infection remains widespread internationally, with a definite morbidity and mortality. The efficacy of standard 7–14 day triple therapies is decreasing, mainly due to increasing primary bacterial resistance to antibiotics. Currently, the most effective treatments are either the sequential regimen or the concomitant therapy. Different patents have been registered showing high bactericidal effects in vitro, some of which are active against clarithromycin- and metronidazole-resistant strains, even at low pH values. Among these novel molecules, benzimidazole-derivatives, polycyclic compounds, pyloricidin, and arylthiazole analogues seem to be the more promising. The identification of essential genes for either bacterial colonization or growth represents a route for potential target therapies in the near future.

Keywords: *Helicobacter pylori* therapy, new antibiotic agents

Introduction

Despite the evidence that *H. pylori* prevalence is declining in developed countries, the infection remains widespread internationally, with a definite morbidity and mortality.[1] Indeed, *H. pylori* is the main cause of nonulcer dyspepsia, peptic ulcer disease, and gastric tumors, including both low-grade mucosa-associated lymphoid tissue lymphoma and adenocarcinoma.[2,3] Among the extra-digestive diseases, data show a significant association between *H. pylori* infection and both idiopathic thrombocytopenic purpura and idiopathic iron deficiency anemia.[4,5] *H. pylori* infection is generally acquired in childhood, and it persists throughout life. Spontaneous resolution is rare, and so a targeted therapy is needed. *H. pylori* colonizes a kind of biological niche – ie, under the gastric mucous layer, strongly attached to epithelial cells and even within cells – where antibiotic action is impaired, and so, curing such an infection is difficult. Different antibiotic combinations, administered together with a proton pump inhibitor (PPI), have been proposed in the last decades. Unfortunately, no available therapy is able to eradicate *H. pylori* in all treated patients. Therefore, new drugs and novel therapeutic approaches are needed.

Current therapies

The combination of a PPI with clarithromycin and amoxicillin or metronidazole is the most common first-line therapy regimen. However, current European guidelines confirm the use of standard 7-day triple therapy only in those areas where primary clarithromycin resistance is lower than 15%–20%, whilst a prolonged 14-day regimen should be used where bacterial resistance rate is higher.[6] Nevertheless, data from two large trials found that after completion of the prolonged 14-day triple therapy,

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the eradication rate was only 70% in nonulcer dyspepsia patients, and 81.7% in peptic ulcer patients.[7,8] Therefore, different therapeutic approaches are needed. The sequential therapy was first introduced in Italy in 2000.[9] This regimen is a 10-day therapy, including a simple dual therapy with a PPI plus amoxicillin 1 g (both twice daily) given for the first 5 days, followed by a triple therapy including a PPI, clarithromycin 500 mg, and tinidazole 500 mg (all given twice daily) for the remaining 5 days.

The first comprehensive, pooled-data analysis of sequential therapy, which included over 1,800 Italian patients, found an eradication rate as high as 93.5%.[10] Moreover, the high efficacy of such a therapy regimen has been confirmed in several other countries, including Israel, Korea, Panama, Poland, Romania, Spain, Taiwan and Thailand, but not in Iran or Latin America.[11–17] Different trials compared the efficacy of sequential therapy with that of standard triple therapies. A meta-analysis showed that a sequential regimen was better than standard 7–10 day triple therapies.[18] These data have been updated, and the eradication rates following the sequential therapy (2,454/2,853; 86%; 95% CI: 84.7–87.3) remained distinctly higher compared to that of triple therapies (2,320/3,079; 75.3%; 95% CI: 73.8–76.9).[19]

Some recent studies found that a levofloxacin- instead of clarithromycin-based sequential therapy also appears highly effective.[20,21] However, such modified sequential therapy precludes the use of a levofloxacin-based second-line therapy, thereby complicating any successive therapeutic approach in patients who fail eradication therapy.[22,23] Moreover, primary resistance to levofloxacin is quickly increasing worldwide, with prevalence values of 17% in Brazil, 16.8% in Belgium, 22.1% in Germany, 18% in Hong Kong, 19.1% in Italy, 14.3% in Japan, and 21.5% in Korea.[22] Therefore, levofloxacin should be used with caution in a first-line therapy regimen.[24]

Concomitant therapy comprises a PPI plus amoxicillin, clarithromycin, and metronidazole, given all together. This therapy was first introduced as an alternative to standard triple therapies more than 10 years ago, and the original duration of therapy was only 5 days. A recent meta-analysis of 15 studies found a high efficacy of this regimen, with an eradication rate of 90%. However, it was noted that the eradication rate increased with therapy duration, being 85% at 3 days, 88% at 4 days, 89% at 5 days, 93% at 7 days, and 92% at 10 days.[25] Another meta-analysis of 9 studies including only 7-day concomitant therapy calculated eradication rates of 90% at ITT and 93% at PP analysis.[26] Pooled estimates of the five randomized controlled trials showed the superiority of concomitant therapy over triple therapy (OR: 2.86; 95% CI: 1.73–4.73).[26]

Future therapies

Although the contributing factors differ,[27] therapy failure mainly depends on primary resistance to different antibiotics (eg, clarithromycin), which is increasing worldwide.[28] It is thought that only new classes of antimicrobials with novel mechanisms of action can fully address the increasing drug resistance.[29] In the last decade, several patents of new antibiotics have claimed potential activity against *H. pylori*.[30–32] Of note, some molecules have shown a very high bactericidal level of activity against *H. pylori* in vitro, including those strains with primary clarithromycin and/or metronidazole resistance. In addition, some molecules preserve antibacterial activity even at low pH values, a clear advantage for *H. pylori* treatment, considering that they must act in gastric acid. In particular, different benzimidazole-derivatives and polycyclic compounds have been patented, which are highly effective against *H. pylori*.[30] Pyloricidin A, B, and C – a family of natural antibiotics – have exhibited a potent and highly selective bactericidal activity against *H. pylori*, with an MIC_{90} value of 0.013 mg/L.[30] In addition, among the arylthiazole analogues, the thienylthiazole derivative 44 exhibited the strongest activity, with MIC_{90} values as low as 0.0065 mg/L.[30] Of note, some isothiazole derivatives have been found to enable a potent inhibition of bacterial urease activity in vitro, constituting a potential "targeted" therapy for *H. pylori* infection.[31] The list of potential useful molecules is provided in Table 1, while in Table 2 there are several plant extracts with anti-*H. pylori* activity in vitro.[30–34] Therefore, it is likely that more powerful drugs will be available in the near future to treat *H. pylori* infection.

Table 1 New molecules with *H. pylori* activity

Molecule	MIC_{90} value (mg/L)	pH activity	Cla-R/ Met-R
Arylthiazole derivative 44	0.0065	NA	NA/NA
Benzimidazole derivatives			
Y-754	0.025	5.5	NA/NA
BAS-118	0.013	NA	Yes/yes
I-valnemulin	0.0125–0.5	NA	Yes/yes
Mupirocin	0.12–0.25	5.4	NA/NA
Polycyclic compound	0.2–0.39	NA	NA/NA
Pyloricidin (A, B, and C)	0.013	NA	NA/NA
Rifampin	0.032–2	NA	Yes/yes

Notes: MIC_{90}: minimal inhibitory concentration; Cla-R: efficacy towards clarithromycin resistant strains; Met-R: efficacy towards metronidazole resistant strains.
Abbreviation: NA, not available.

Table 2 Some plant extracts with potential anti-*H. pylori* activity in vitro

Plant source	Source or molecule	MIC_{90} (mg/L)
Barringtonia acutangola	Leaf	25
Cassia grandis	Leaf	50
Cleome viscosa	Leaf	50
Cycas siamensis	Leaf	100
Hypericum perforatum	*L. Hyperforin*	15.6–31.2
Hyptis fasciculata	Cirsilineol/Cirsimaritin	3.2–6.3
Kaempferia galanga	Rhizome	25
Litsea elliptica	Leaf	100
Maleleuca quinquenervia	Leaf	100
Mallotus philippinensis	Rottlerin	3.12–6.25
Myristica fragrans	Aril	12.5
Myristica fragrans	Leaf	50
Pistacia lentiscus	Triterpenic acids	0.139
Pouzolzia pentandra	Leaf	100
Syzygium aromaticum	Leaf	50
Vitis vinifera	Resveratrol	6–12.5
Xanthium brasilicum	Xanthanolide	13.2–250
Zingiber officinale	Rhizome	0.78–12.5

Abbreviation: MIC_{90}, minimal inhibitory concentration.

Many studies have addressed the identification of novel therapeutic targets (eg, bacterial proteins, mechanisms, genes required for growth and/or colonization, etc). Further investigation of anti-*H. pylori* therapies have addressed the identification of essential genes required for in vitro bacterial survival, or genes essential for mucosal colonization.[35,36] Indeed, several studies have shown large numbers of genes involved in cellular motility that are required for colonization or growth, demonstrating that they represent a potential target by *H. pylori*-specific anti-infective agents. Additional functions potentially susceptible to therapeutic intervention include cellular processes like chemotaxis, protein folding, regulation, genetic information processing, and resistance to acid and oxidative stresses.[37] There are several genes that have been evaluated as potential therapeutic targets, most of them encoded for proteins which form biochemical pathways, or urease–related genes that are essential for host colonization. There are also many gene-encoding proteins required for bacterial growth that have been studied as potential therapeutic targets, but further evaluations are needed.[38]

Conclusion

The available antibiotics active against *H. pylori* in vivo are very rare, and new molecules are needed. The current most effective combination of these drugs is both sequential and concomitant therapy. Different patents have been registered showing high bactericidal effects in vitro, some of which are active against clarithromycin- and metronidazole-resistant strains, even at low pH values. Therefore, the search for novel antibacterial therapies against *H. pylori* is a "work in progress" driven by the goal of preventing gastric cancer, and by worldwide increasing antibiotic resistance.

Disclosure

The authors reports no conflicts of interest in this work.

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