

PhD research activity – 1st Annual Progress Report

Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Prof. Carmelo Scarpignato.

During the first year of my PhD course the research activity has been mainly focused on five issues.

First: to evaluate the efficacy and the safety of rifaximin, a poorly absorbable antibiotic, with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganisms, both aerobes and anaerobes to eradicate the Small Intestine Bacterial Overgrowth (SIBO) performing a systematic review and meta-analysis. SIBO is a condition caused by an increased number and/or abnormal type of bacteria in the small bowel. An extensive research of 3 databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials [CENTRAL]) was performed. Furthermore, abstracts from the major American, European and Asiatic gastroenterology meeting were also searched. The preliminary findings of this study showed that rifaximin is effective for treating SIBO, with an efficacy that appears to be dose and time. These results have been presented as *poster* (accepted through a peer-reviewed process) to the FISMAD (Federazione Italiana Società Malattie Apparato Digerente - held in Naples, March 19 - 22, 2014) and to the Digestive Disease Week (held in Chicago, Illinois, USA, May 3 - 6, 2014).

Secondly: to evaluate the Number Needed to treat (NNT) and the Number Needed to Harm (NNH) for prucalopride, at the recommended dose (2 mg daily), in randomized clinical trials (RCTs), carried out in patients with chronic constipation. Prucalopride is the first selective, high-affinity 5-HT₄ agonist, without any significant activity towards other (5-HT and non 5-HT) receptors or channels (e.g. the human Ether-à-go-go-Related Gene - hERG) at the therapeutic doses. In vitro binding studies have shown that its affinity towards the hERG is more than 250 times lower than that displayed against 5-HT₄-receptors. The outcomes assessed (at 12 weeks) were the number of patients with an average increase of ≥ 3 SCBM, the number of patients with an average increase of ≥ 1 SCBM or SBMs as well as increase of QT corrected according to Bazett's Formula (QTcB) > 500 ms in patients that had a baseline QTcB < 450 ms. An extensive research of 3 databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials [CENTRAL]) was performed. Furthermore, abstracts from the major American, European and Asiatic gastroenterology meeting were also searched. The preliminary findings showed that NNH for QTcB prolongation largely exceeds the NNT for each of the efficacy end-points analysed, confirming experimental data that suggested that, at clinically relevant concentrations, prucalopride is unlikely to block hERG channels. These results have been presented as *oral presentation* (accepted through a peer-reviewed process) to the FISMAD (Federazione Italiana Società Malattie Apparato Digerente - held in Naples, March 19 - 22, 2014) and as *poster* to the Digestive Disease Week (held in Chicago, Illinois, USA, May 3 - 6, 2014).

Thirdly: we aimed to evaluate whether efficacy of Sequential Therapy (ST) to eradicate *Helicobacter pylori* infection in naïve patients in RCTs performed in Europe was similar to that obtained in other Continents, through a systematic review and meta-analysis of the available RCTs. Sequential therapy (ST), is a regimen giving antimicrobials (with proton pump inhibitors) in sequence rather than all simultaneously to eradicate *Helicobacter pylori* infection, was first studied in Italy and Europe and subsequently in other Continents. An extensive research of 3 databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials [CENTRAL]) was performed. Furthermore, abstracts from the major American, European and Asiatic gastroenterology meeting were also searched. The preliminary findings showed that Eradication rates with ST are similar in Europe, Asia and Africa, and the lower rates observed in South America are mirrored – in the comparative trials – by similarly lower success rates of other regimens (namely triple or concomitant therapies), likely reflecting the higher prevalence of antimicrobial resistance. These results have been presented as *oral presentation* (accepted through a peer-reviewed process) to the FISMAD (Federazione Italiana Società Malattie Apparato Digerente - held in Naples, March 19 - 22, 2014) and as *poster* to the Digestive Disease Week (held in Chicago, Illinois, USA, May 3 - 6, 2014).

Fourthly: we re-assessed a clinical and economic evaluation of tapentadol extended release and oxycodone/naloxone extended release in comparison with controlled release oxycodone in musculoskeletal pain recently published (Coluzzi F, Ruggeri M. *Clinical and economic evaluation of tapentadol extended release and oxycodone/naloxone extended release in comparison with controlled release oxycodone in musculoskeletal pain. Curr Med Res Opin* 2014;30:1139-51). Tapentadol is the first US FDA approved centrally acting analgesic having both μ -opioid receptor agonist and noradrenaline reuptake inhibitory activity with minimal serotonin reuptake inhibition. The oxycodone/naloxone combination (both compounds included in an oral extended-release formulation in a 2:1 fixed dose ratio) represents a new approach to counteract opioid induced constipation, while maintaining effective analgesia. Following its release, naloxone acts locally on the gut, antagonizing the opioid binding to m-receptors. After being absorbed in parallel with

oxycodone, naloxone is rapidly and completely inactivated through a high first-pass effect in the live. The experience with both medications is limited and these two approaches toward improved pain management have not to date been directly compared. We discussed in detailed the several methodological and clinical pitfalls affecting this study, questioning therefore the validity and the clinical relevance of this study. Our work was submitted as "Letter to the Editor" and published after a peer-reviewed process.

Fifth. Treatment with anti-TNF has been recognized as a risk factor for tuberculosis (TB) reactivation. We evaluated the risk of tuberculosis (TB) reactivation in rheumatologic and non-rheumatologic patients treated with tumour necrosis factor antagonists (anti-TNF) with and without concomitant therapies. An extensive research of 3 databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials [CENTRAL]) was performed. It was found that TB risk with anti-TNF agents appeared to be increased when these agents were used in combination with methotrexate or azathioprine as compared with monotherapy regimen. TB risk seemed also to be higher than placebo, even when monotherapy is prescribed. These results have been published as full article after a peer reviewed process.

Articles (Peer-Reviewed):

Scarpignato C, Gatta L. Comparing tapentadol to oxycodone/naloxone combination: building castles in the air. *Curr Med Res Opin* 2014; 1-4.

Lorenzetti R, Zullo A, Ridola L, Diamanti AP, Lagana B, Gatta L, Migliore A, Armuzzi A, Hassan C, Bruzzese V. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. *Annals of Medicine* 2014; 46: 547-554.

Conference Proceedings (Peer-Reviewed):

Gatta L, Scarpignato C. OC.05.4 Cardiac safety of prucalopride in randomized clinical trials of patients with chronic constipation. *Digestive and Liver Disease* 2014; 46 (Supplement 2): S14. (*Oral Communication*)

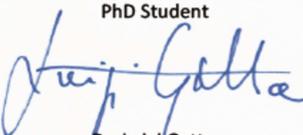
Gatta L, Vaira D, Scarpignato C. OC.06.5 Is sequential therapy for eradication of helicobacter pylori equally effective all over the world? A meta-analytic approach. *Digestive and Liver Disease* 2014; 46 (Supplement 2): S17. (*Oral Communication*)

Gatta L, Scarpignato C. P.18.7 Dose- and time-dependent eradication of small intestine bacterial overgrowth (sibo) with rifaximin: a meta-analytic approach. *Digestive and Liver Disease* 2014; 46 (Supplement 2): S129. (*Poster*)

Gatta L, Scarpignato C. Sa2022 Does Prucalopride Have a Pro-Arrhythmic Potential? Lessons From Randomized Clinical Trials in Chronic Constipation. *Gastroenterology* 2014; 146 (Supplement 1): S357. (*Poster*)

Gatta L, Vaira D, Scarpignato C. Su1191 Efficacy of Sequential Therapy for Eradication of Helicobacter pylori All Over the Word. Lessons From a Comparative Meta-Analysis. *Gastroenterology* 2014; 146(Supplement 1): S398-S399. (*Poster*)

Gatta L, Scarpignato C: Su1423 Eradication of Small Intestine Bacterial Overgrowth With Rifaximin: A Doseand Time-Dependent Effect. *Gastroenterology* 2014, 146(5, Supplement 1): S465. (*Poster*)

PHD Student

Dr. Luigi Gatta

The Supervisor

Prof. Carmelo Scarpignato

PhD CME/CFU – 1st Annual Progress Report

Student's Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Professor Carmelo

Date	Title	CME
April 2014	Globesity and Its metabolic and Digestive Consequences	8.5
May 2014	Le Basi della Nutrizione Artificiale in Ospedale e a Domicilio	18
September 2014	Update sulla Malattia Diverticolare e Presentazione del Registro REMaD	7
October 2014	I Corso di Nazionale di Ecografia Clinica SIEMC	25,5
Total		59
	Research Activity	CFU
	Overall research activities	54

PhD Student
Luigi Gatta, M.D.

Supervisor
Prof. Carmelo Scarpignato

PhD research activity – 2nd Annual Progress Report

Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Prof. Carmelo Scarpignato.

During the second year of my PhD course the research activity has been mainly focused on XXX issues.

First: I have attended a high level international course (not funded by University of Parma) entitled “*Indirect comparisons and network meta-analysis: Evidence synthesis with multiple treatments*” hold by Prof. Julian Higgin (course co-ordinator, from the Department of Hygiene and Epidemiology, University of Bristol, UK) and by Dr. Anna Chaimani and Dr. Orestis Efthimiou (Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Greece), organized by the Institute of Social and Preventive Medicine ISPM, University of Bern, and which took place in Wengen, Switzerland, 18-21 January 2015.

Standard meta-analysis methods for clinical trials focus on comparisons of two interventions, such as a drug versus a placebo, or a new intervention versus standard practice. Rarely are there only two interventions under consideration in clinical practice. Extensions of meta-analysis to address three or more treatments have been the subject of much methodological research in recent years, and are increasingly being applied. At simplest, indirect comparisons can be performed in ways that respect the randomization within each clinical trial. More complex are so-called network meta-analyses, also known as multiple treatments meta-analyses or mixed treatment comparison meta-analyses. These allow the simultaneous analysis of clinical trials involving different treatments. This course was aimed at statisticians, epidemiologists and other quantitatively-minded researchers who want to understand state-of-the-art statistical syntheses of clinical trials involving multiple interventions.

Secondly: under the guidance and in collaboration with my supervisor, Prof. Scarpignato, I was (and still am) involved in a scientific project on behalf of *Italian Society of Pharmacology (SIF)*, *Italian Association of Hospital Gastroenterologist and Endoscopist (AIGO)*, and with the participation of *Italian Federation of General Practitioner (FIMMG)*. The aim of this was is to assess the appropriate use of Proton Pump Inhibitors (PPIs) in clinical practice based on the best available evidence published in literature. To best of our knowledge, this is the first time that a scientific project with this aim is attempted. PPIs are registered for the treatment of upper gastrointestinal disorders, such as peptic ulcer disease (and gastro-esophageal reflux disease. In addition, PPIs are recommended for the prevention of gastrointestinal side effects owing to the use of non steroidal anti-inflammatory drugs. In the literature, inappropriate prescription of PPIs has been reported, with both overutilization as well as underutilization. Numerous risks have been also associated with prolonged and potentially non-judicious use of PPIs. Medications that are pH-dependent for appropriate absorption can be affected by PPIs, resulting in increased rates of absorption. Such medications include ketoconazole, digoxin, nifedipine, indinavir, midazolam, didanosine, methadone, and aspirin. Several cases of hypomagnesemic hypoparathyroidism associated with long-term use of PPIs have been reported. Use of PPIs for 12 or more months seem to associated with vitamin B₁₂ deficiency, yet no association has been found between either past or short-term PPI therapy. *Clostridium difficile*-associated diarrhoea, community-acquired pneumonia, and hip fractures have all been found to have a statistically significant association with current and/or long-term PPI use. This multidisciplinary team is actually reviewing a considerable amount of literature to be able to give clear directions on the prescription of the inhibitors, the potential risks associated with the chronic administration, and to avoid indications prescription. The preliminary presentation of the results of this project will be made during the next FISMAD (Federazione

Italiana Società Malattie Apparato Digerente) meeting that will take place in Naples, 24-27 February 2016.

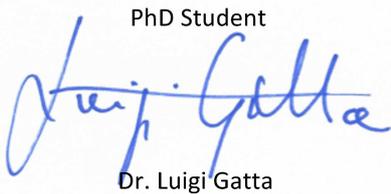
Thirdly: we aimed to assess the prevalence of resistant strains to clarithromycin (Cla) and metronidazole (Metro) in a cohort of naïve patients performing EGDS for dyspeptic symptoms and to evaluate also how the resistance to antimicrobial agents changed during the years and if there was a correlation with the prescription of medication during those year. This research was performed in association with the Department of Medical and Surgical Sciences of the University of Bologna, where the EGDS and cultures were performed. The preliminary results of this project have been presented at the FISMAD (Federazione Italiana Società Malattie Apparato Digerente) meeting that took place in Bologna, 25-28 March 2015 and accepted as oral communication.

Fourthly: we have almost finalized a proportion meta-analysis to evaluate the Efficacy of Rifaximin (a poorly absorbed, GI-targeted, antibiotic) in the Eradication of Small Intestinal Bacterial Overgrowth (SIBO). The paper is going to be submitted shortly.

Conference Proceedings (Peer-Reviewed):

Gatta L, Fiorini G, Castelli V, Saracino I, Ricci C, Zullo A, Scarpignato C, Vaira D. OC.07.2 antimicrobial susceptibility pattern and its influence on the effectiveness of sequential therapy: results from a referral center. Digestive and Liver Disease 2015; 47S: e87. (Oral Communication)

PhD Student

A handwritten signature in blue ink, appearing to read 'Luigi Gatta', written in a cursive style.

Dr. Luigi Gatta

The Supervisor

A handwritten signature in blue ink, appearing to read 'Carmelo Scarpignato', written in a cursive style.

Prof. Carmelo Scarpignato

PhD CME/CFU – 2nd Annual Progress Report

Student's Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Professor Carmelo Scarpignato

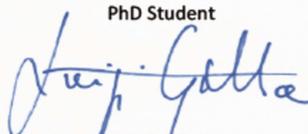
Date	Title	CME
January 2015	Indirect comparisons and network meta-analysis: Evidence synthesis with multiple treatments	1,5
March 2015	21° Congresso Nazionale delle Malattie Digestive	10
April 2015	Extra-Digestive GRED: What's next	7.5
November 2015	Percorsi diagnostici terapeutici dei pazienti con Spa-IBD	7.9
Total		26.9

Research Activity

CFU

Overall research activities

52

PhD Student

Dr. Luigi Gatta

The Supervisor

Prof. Carmelo Scarpignato

PhD research activity – 3rd Annual Progress Report

Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Prof. Carmelo Scarpignato.

During the third year of my PhD course the research activity has been mainly focused on six issues.

Firstly, under the guidance and in collaboration with my supervisor, Prof. Scarpignato, the project started in 2015 on behalf of *Italian Society of Pharmacology (SIF)*, *Italian Association of Hospital Gastroenterologist and Endoscopist (AIGO)*, and with the participation of *Italian Federation of General Practitioner (FIMMG)*, whose aim was to assess the appropriate use of Proton Pump Inhibitors (PPIs) has been published in a peer reviewed journal (*BMC Medicine*)¹. The multidisciplinary team reviewed and distilled an extensive amount of literature in order to give clear directions on the appropriate prescription of PPIs and the potential risks associated with the chronic administration.

Secondly, a systematic review and meta-analysis concerning the efficacy and the safety of rifaximin to treat the Small Intestinal Bacterial Overgrowth (SIBO) was completed and *submitted to a peer reviewed journal*². Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel, and it is a well-recognized cause of maldigestion and malabsorption. Rifaximin is a product of synthesis experiments designed to modify the parent compound, rifamycin, in order to achieve low gastrointestinal absorption while retaining good antibacterial activity. Both experimental and clinical pharmacology have clearly shown that this compound is a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganism, both aerobes and anaerobes. Over the past decades, rifaximin has been largely used to treat SIBO even if there is currently a lack of a critical summary of evidence. To bridge this gap, a systematic review and meta-analysis of randomized and non-randomized studies was performed to evaluate the clinical effectiveness of and safety rifaximin to eradicate SIBO in adult patients. The result of this meta-analysis showed that rifaximin treatment seems to be effective and safe for the treatment of SIBO. However, since the quality of the available studies is generally poor, well-designed RCTs are needed to substantiate these findings and to establish the optimal regimen.

Thirdly, I was involved in a project with the Department of Medical and Surgical Sciences of the University of Bologna to assess the efficacy and safety of a rifabutin triple therapy to manage the infection in patients harboring multidrug-resistant strains of *Helicobacter pylori (H. pylori)*. Eradicating *H. pylori* in patients harboring multidrug-resistant strains is very difficult. Both empiric and tailored therapy (based on culture and antibiotic sensitivity testing) are extremely difficult in these patients due to the paucity of effective agents. In addition, culture and antimicrobial sensitivity testing is not generally available in many parts of the world including the United States. Rifabutin is a rifamycin derivative, which has very high bactericidal activity against *H. pylori* strains, and primary resistance against this drug is very low (< 2%). This study showed that 12-day low-dose rifabutin/high-dose proton pump inhibitor regimen is a safe and reliable option for patients infected with triple-resistant strains. The results of this study were published in peer-reviewed journal³.

Fourthly, I was involved in an international project whose aim was to assess the diagnostic concordance between endoscopic and histological atrophy in the United Kingdom and Japan. The results of this study showed that endoscopic grading can predict histological atrophy with few false negatives, indicating that precancerous conditions can be identified during screening endoscopy, particularly in patients in western countries. The results of this study were published in peer-reviewed journal⁴.

Fifthly, we were involved in a project with the Department of Medical and Surgical Sciences of the University of Bologna to assess the efficacy and safety of a new single capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride (namely Pylera[®]) recently introduced as 10-day regimen in association to proton pump inhibitor to eradicate *H. pylori* infection in

naïve patients. The results of this study were submitted as communication to the *Digestive Disease week 2017 (Peer-Reviewed Conference Proceedings)*⁵.

Sixthly, we reported a series of three cases of acute pancreatitis in young women taking Ethinylestradiol/Levonorgestrel as oral contraceptive. This case series was submitted as communication to the *FISMAD (Federazione Italiana Società Malattie Apparato Digerente) 2017 (Peer-Reviewed Conference Proceedings)*⁶.

Articles (Peer-Reviewed):

¹Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. *BMC Medicine* 2016; 14 doi.org/10.1186/s12916-016-0718-z.

²Gatta L, Scarpignato C. Systematic Review and Meta-analysis: Is Rifaximin Effective for the Treatment of Small Intestine Bacterial Overgrowth? *Submitted for publication*.

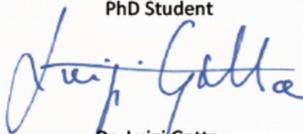
³Fiorini G, Zullo A, Vakil N, Saracino IM, Ricci C, Castelli V, Gatta L, Vaira D. Rifabutin Triple Therapy is Effective in Patients With Multidrug-resistant Strains of *Helicobacter pylori*. *Journal of Clinical Gastroenterology*. 2016: doi.org/10.1097/MCG.0000000000000540.

⁴Kono S, Gotoda T, Yoshida S, Oda I, Kondo H, Gatta L, Naylor G, Dixon M, Moriyasu F, Axon A. Can endoscopic atrophy predict histological atrophy? Historical study in United Kingdom and Japan. *World Journal of Gastroenterology* 2015; 21: 13113-23.

Conference Proceedings (Peer-Reviewed):

⁵Gatta L, Fiorini G, Saracino IM, Scarpignato C, Vaira D. Effectiveness and Safety of first line 10-day triple pill (Pylera®) in combination with PPIs for the eradication of *H. pylori* infection in naïve patients. *Submitted to the Digestive Disease Week 2017*.

⁶Gatta L, Corti F, Giunta S, Ceccareli G, Scarpignato C. Ethinylestradiol/Levonorgestrel Oral Contraceptive and Acute Pancreatitis: a cases report. *Submitted to the FISMAD 2017*.

PhD Student

Dr. Luigi Gatta

The Supervisor

Prof. Carmelo Scarpignato

PhD CME/CFU – 3rd Annual Progress Report

Student's Name: Luigi Gatta, M.D.

PhD cycle: XXIX

Research topic: Evidence Based Medicine and Pharmacology.

Supervisor: Professor Carmelo Scarpignato

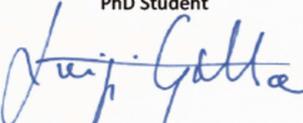
Date	Title	CME
January 2016	Systematic Review and Meta-Analysis of Diagnostic test Accuracy	1,5
June 2016	V Italian IBD Course	11
September 2016	IBD DESTINATION FORWARD	14
October 13-15 2016	Pain Management, The Science Behind	9
October 15-19 2016	24 th United European Gastroenterology Week	17
October 28 2016	Sliding Doors	9.2
Total		61.7

Research Activity

CFU

Overall research activities

52

PhD Student

Dr. Luigi Gatta

The Supervisor

Prof. Carmelo Scarpignato