Progress Report

Use of biosimilars in inflammatory bowel disease: Statements of the Italian Group for Inflammatory Bowel Disease

Vito Annese a,*, 1, Maurizio Vecchi b,*, 1, on behalf of the Italian Group for the Study of IBD (IG-IBD) 2

* Department of Medical and Surgical Specialties, Gastroenterology, AOU University Hospital Careggi, Florence, Italy
b University of Milan, Department of Biomedical Sciences for Health, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

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ABSTRACT

The introduction of biological therapies, particularly anti-TNFα agents, has revolutionized the management of inflammatory bowel disease in those cases which are refractory to conventional treatment; however these drugs are not risk-free and their use has substantially increased the cost of treatment. As marketing protection expires for original, first-generation biopharmaceuticals, lower-cost “copies” of these drugs produced by competitor companies—referred to as biosimilars—are already entering the market. In September 2013, the European Medicines Agency approved two infliximab biosimilars for treatment of adult and paediatric inflammatory bowel disease patients, a decision based largely on efficacy and safety data generated in studies of patients with ankylosing spondylitis and rheumatoid arthritis. For many clinicians, extrapolation practices and the general question of interchangeability between biosimilars and reference biologics are cause for concern. In the present paper, the Italian Group for inflammatory bowel disease presents its statements on these issues, with emphasis on the peculiar clinical characteristics of inflammatory bowel disease and the importance of providing physicians and patients with adequate information and guarantees on the safety and efficacy of these new drugs in the specific setting of inflammatory bowel disease.

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1. Introduction

Biological medicinal products (or biologics) are characterized by active substances derived from living cells or organisms with the aid of biotechnology methods (recombinant DNA, controlled gene expression, antibody technologies) [1]. The first-generation biologics were launched in the late 1970s and early 1980s, and this innovative class of drugs is now one of the fastest growing sectors of the pharmaceutical industry [2]. In the field of inflammatory bowel diseases (IBD), the therapeutic use of monoclonal antibodies (mAbs), particularly those directed against tumour necrosis factor α (TNFα), has allowed physicians to set and achieve more ambitious therapeutic targets [3,4], however these drugs are not without risk [5], and their use has also markedly increased the direct costs of medical treatment of IBDs [6]. Data exclusivity and market protection for many of the original biologics (e.g., erythropoietins, gonadotropins, human insulins) are currently expiring in various parts of the world, and competitors are already seeking authorization to market “copies” of these agents. Referred to collectively as biosimilars, follow-on biologicals, or subsequent-entry biologicals, these new drugs are expected to be considerably less expensive than the originals [2]. In the European Community, marketing authorization for biosimilars is granted in accordance with guidelines established in 2005 by the European Medicines Agency’s (EMAs) Committee for Human Medicinal Products (CHMP) [7,8] and integrated in 2012 with specific guidance for biosimilar mAbs [9]. Biosimilar drugs have also been identified as a topic for regular exchange of information and collaborative meetings by the EMA and United States Food and Drug Administration (FDA) [10].

The anti-TNFα mAb infliximab was the first biologic agent used to treat Crohn’s disease (CD) and ulcerative colitis (UC), and it is still the one most widely used for this purpose. Its patent protection expires in Europe between 2013 and 2015, depending on the country [11], and in September 2013 the EMA approved two infliximab
biosimilars that had been licensed for use in India and South Korea in 2012 [12]. Although infliximab biosimilars are expected to reduce the cost of IBD treatment, questions are being raised regarding the degree to which biosimilars can be considered interchangeable with their respective reference biologics. Particular concern has been expressed over the authorization for treatment of IBD based on data extrapolated from studies conducted in autoimmune diseases [13–15].

In this paper, the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) outlines its official position on the use of biosimilar agents in the treatment of IBD. Emphasis is placed on the peculiar characteristics of IBD (see statements #5, 6, 8, and 9), and the current lack of validated biomarkers for assessing disease activity, responsiveness to treatments, and the efficacy of therapy.

2. Biosimilars

Unlike chemical generics, biosimilars cannot be considered mere copies of the original reference drug. The characteristics and properties of drugs containing biotechnology-derived proteins depend largely on the type of cell in which they are produced, the production and purification processes, and the methods used to transform them into drugs. Subtle differences involving a single step in the production process—even the plant location can translate into major differences in terms of pharmacokinetics, treatment efficacy, and/or safety. Some degree of divergence between the reference drug and biosimilar manufacturing processes is inevitable because, even after patent expiration, the reference agent manufacturer is not obliged to reveal details of its production practice. However, the same caveat applies to post-marketing changes/improvements in the process used to manufacture any given biologic. The production process for the original version of infliximab (Remicade™), for example, has undergone over 30 major or minor modifications since the drug was first licensed, and each has had to be assessed by the EMA and other regulatory authorities to ensure the comparability of the pre- and post-change products [16]. Verification of comparability is especially important for mAbs, which are high-molecular-weight proteins with complex secondary and tertiary structures that often undergo post-translational modifications, such as glycosylation. Indeed, covalent modifications of these complex proteins, including phosphorylation, SUMOylation, O-GlcNAcylation, and ubiquitylation, represent key mechanisms for regulating the protein’s stability and transcriptional activity.

For these reasons, marketing authorization for a biosimilar is granted only after the applicant has reliably demonstrated the innovator product’s equivalence with the reference biological agent in terms of quality, efficacy, and safety. For the EMA, this is generally accomplished with a step-wise comparability exercise, which includes in vitro experiments followed, when necessary, by in vivo studies. Only when these pre-clinical studies have generated sufficient evidence of the two drugs’ pharmacotoxicological comparability (including structural characteristics, physicochemical properties, purity and impurities, biological activity) is clinical testing undertaken to ensure comparability at the levels of pharmacokinetics, pharmacodynamics, efficacy, and safety, with special emphasis on potential immunogenicity [2]. Full equivalence cannot be demonstrated without the aid of extremely large clinical trials, but the innovator drug must display comparability with the reference drug that falls within pre-specified and well-justified clinical margins established by the EMA [17].

Authorization of biosimilars—as for all drugs—must be based on data generated in clinical studies large enough to provide a comprehensive profile of the new agent’s safety profile. This entails comparison of the nature, severity, and frequency of the biosimilar’s adverse effects with those of the reference product. Collection of post-approval safety data is also essential for these drugs. Both the EMA and FDA require pharmacovigilance programmes for biosimilars, with continuous monitoring of safety issues to ensure timely, appropriate responses if problems arise [18].

Once a biosimilar has been approved by the EMA for use in a given indication, efficacy and safety data may be extrapolated to other indications approved for the reference drug, even though the biosimilar agent has not been formally tested in that setting [7]. This practice is more common when the drug’s mechanism of action in the different diseases is the same or similar (i.e., immunosuppression). However, additional data may well be needed to justify the extrapolation if, for example, the reference drug’s actions in the two diseases involve different sites of the molecule or of the target cells or if its safety profiles in the two settings are different [7]. In addition, a potential concern with the practice of data extrapolation is that use of a biopharmaceutical may be associated with different risks in different patient populations (e.g., patients with different diseases, different age groups).

It is important to note that the EMA’s assessment of biosimilar medicines is done exclusively to the purposes of marketing authorization. The agency takes no stance on the question of whether or not the biosimilar should be used interchangeably with its reference medicine. Indeed, it suggests that such decisions be made by qualified healthcare personnel on the basis of national or local guidelines [14]. The Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) has recently taken a step further, recommending that the decision to prescribe a biosimilar drug or its reference drug be made exclusively by the specialist managing the specific disease [19]. Clinicians must thus be aware of the basis of a biosimilar drug’s approval for a given indication, and they must be free to make informed treatment choices with their patients on the use of such drugs.

3. Biologics in inflammatory bowel disease

Therapeutic mAbs have become a fundamental tool for the management of numerous diseases. Over 300 products of this type are currently under development, and approximately 30 others have already been approved in the United States [20]. One of the most effective and widely used classes of therapeutic mAbs are the anti-TNFα agents, which are used in the treatment of rheumatic diseases (e.g., rheumatoid arthritis [RA], ankylosing spondylitis [SA], as well as for IBD. Indeed, four of the biologics currently approved by the EMA and FDA for the treatment of IBD are anti-TNFα mAbs (infliximab, adalimumab, golimumab, and certolizumab, which has only FDA approval). The other two are anti-integrin mAbs (natalizumab, which is directed against integrin α4β1 and was authorized by the FDA in 2004, and the new anti-α4β7-integrin vedolizumab, which has been recently approved for treatment of IBD in both Europe and the United States).

Table 1 summarizes the results of the American College of Gastroenterology’s recent meta-analysis and systematic review of placebo-controlled studies on the efficacy of anti-TNFα and natalizumab therapy in adults with IBD [21]. Data are expressed as failure to achieve remission at 4–12 weeks.

Significant heterogeneity has emerged between anti-TNFα agents (P = 0.007) in terms of their efficacy in active CD: the best results were achieved with infliximab (number needed to treat, NNT = 4) and adalimumab (NNT = 7), whereas the difference between certolizumab and placebo displayed only borderline statistical significance. However, for preventing relapse of quiescent luminal CD, two trials found that adalimumab was not significantly better than placebo. The benefit of infliximab in fistulizing CD was documented only in the single trial in which fistula healing was
Table 1

Summary of meta-analyses and systematic review of placebo-controlled studies on the efficacy of anti-TNFα and natalizumab therapy in adults with inflammatory bowel disease (modified from Ref. [23]). Data expressed as failure to achieve remission at 4–12 weeks.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Trials (n)</th>
<th>Patients (n)</th>
<th>Setting</th>
<th>Number need to treat</th>
<th>Relative risk of failure</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNFα</td>
<td>10</td>
<td>2756</td>
<td>Active luminal CD</td>
<td>8</td>
<td>0.87</td>
<td>0.8–0.94</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>5</td>
<td>1771</td>
<td>Active luminal CD</td>
<td>11</td>
<td>0.88</td>
<td>0.8–0.94</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>5</td>
<td>1390</td>
<td>Maintaining remission in CD</td>
<td>4</td>
<td>0.71</td>
<td>0.6–0.76</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>6</td>
<td>453</td>
<td>Fistulating CD</td>
<td>–</td>
<td>0.88</td>
<td>0.7–1.05</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>1</td>
<td>94</td>
<td>Fistulating CD*</td>
<td>3</td>
<td>0.62</td>
<td>0.48–0.81</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>5</td>
<td>827</td>
<td>Active UC</td>
<td>4</td>
<td>0.72</td>
<td>0.57–0.91</td>
</tr>
</tbody>
</table>

TNF, tumour necrosis factor; NNT, number need to treat; RR, relative risk; CL, confidence interval; CD, Crohn’s disease; UC, ulcerative colitis.

* The only trial on fistulating CD as inclusion criteria [14].

the primary outcome [22], but the method used to define this outcome in this study has been questioned [23]. A more recent study that was not included in the meta-analysis looked at the efficacy of adalimumab in 494 patients with active UC [24]. Failure to achieve remission at 8 weeks was significantly less common in patients treated with adalimumab (83.5% vs. 90.7% in the placebo group, P = 0.019), especially in those who were anti-TNFα naïve (78.7% vs. 89% with placebo; P = 0.017).

Areas for improvement and unresolved issues are by no means lacking. First of all, while current treatment with anti-TNFα agents often produces clinical improvement in patients with IBD, no more than one third achieve true remission, and in many cases the response is only temporary. Given the life-long nature of these diseases, there is a real need for novel therapies that target components of the pathogenic response other than the adaptive immune system (e.g., those that boost innate immunity or block leukocyte infiltration [reviewed in Ref. [25]]). Second, although over a decade has passed since their introduction, the currently licensed anti-TNFα agents have still not been subjected to controlled, head-to-head comparison, and there is still no widespread consensus on the optimal duration of therapy with these drugs, its possible discontinuation, and the risk/benefit ratio of its use with azathioprine. It is also important to recall the wide variability that characterizes the clinical features of IBD and the response to anti-TNFα mAbs. Optimization of treatment and reduction of its cost would thus be facilitated if we had validated subclinical markers capable of predicting drug responsiveness and a more accurate and widely used method for measuring anti-drug antibodies and drug trough levels [26–29].

As far as biosimilars are concerned, two innovator infliximabs (Inflectra [Hospira, Inc., Lake Forest, IL] and Remsima [Celltrion Inc., South Korea]) have been authorized for the treatment of autoimmune diseases and IBD in India and South Korea since 2012 [30]. Data on Inflectra’s efficacy and safety in the former setting come mainly from two large trials. The PLANETAS study [31] was a randomized, phase II, double-blind trial comparing CT-P13 (Inflectra™) and infliximab 3 mg/kg in 250 patients with ankylosing spondylitis (AS). At 30 weeks, the pharmacokinetic profiles of the two agents (the primary focus of this trial) were judged to be equivalent. The two agents also displayed comparable efficacy and safety profiles. Infusion reactions occurred in 3.9% of the patients treated with CT-P13 (vs. 4.9% in the infliximab group), and 27.4% of the patients developed anti-drug antibodies (vs. 22.5% of those on infliximab). In the phase III double-blind PLANETRA trial [32], 604 patients with rheumatoid arthritis (RA) were randomized to CT-P13 or infliximab 3 mg/kg (both given with methotrexate). Again, at 30 weeks, the two treatment groups presented very similar rates of American College Rheumatology 20% responses (the primary endpoint) (60.9% vs. 58.6%, respectively), drug-related adverse events (35.3% vs. 35.9%), and anti-drug antibodies (48.4% vs. 48.2%).

In September 2013, on the basis of these findings and the other data presented by the sponsors, the EMA approved both biosimilars for treatment of RA, AS, and psoriatic arthritis, as well as for adult and paediatric IBD. The latter decision was supported by extrapolation of data reported in the PLANETAS and PLANETRA studies, the results of a small study of 25 IBD patients and a number of in vitro experiments. At the time of this writing, however, no post-marketing data have been published on the efficacy and safety of either of these agents in IBD (not even in abstract form).

These findings are encouraging, but previous experience with licensed biological drugs has demonstrated that a drug’s proven efficacy in autoimmune diseases does not always predict its efficacy and/or safety in IBD [33]. Indeed, in its recent assessment of Inflectra, Health Canada [34] found that “scientific rationales submitted by the sponsor were adequate to support extrapolation [of the data acquired in studies of RA and AS] to the indications and uses pertaining to psoriatic arthritis and plaque psoriasis, [but] extrapolation to indications and uses pertaining to Crohn’s disease and ulcerative colitis could not be recommended due to differences between Inflectra and the reference product, that could have an impact on the clinical safety and efficacy of these products in these indications.”

4. Statements

The IG-IBD stresses the importance of offering IBD patients the best treatment available along with adequate information about safety; compromises based on short-term economic scenarios should be avoided. However, decisions on the authorization and use of biosimilar therapy for IBD must be made in accordance with the principle of rational use of the finite resources of the national health system. To promote such decision-making, the IG-IBD decided to issue a consensus statement on this topic. Two group members, V.A. and M.V., reviewed the literature and drafted a preliminary version of the statements. The latter were then revised, in accordance with Delphi methodology, during two rounds of online voting by members of the IG-IBD Governing Board and 16 IG-IBD members who had been involved in drafting the group’s 2011 Clinical Practice Guidelines [4]. Given the high degree of agreement by these members, no face-to-face meeting was held. The statements are not intended as practical recommendations for management: they are merely expert opinions designed to inform the debate within the scientific community and possibly the regulatory agencies. For this reason, the statements are not accompanied by evidence levels or grades of recommendations but only by the percentage of voting members expressing full agreement (in brackets).

4.1. Background

Biosimilars are copies of a previously licensed biologic drug, which enter the market after the original product’s market protection has expired. Although the action of a biosimilar drug is intended to be equivalent to that of the original reference product, the complex structures of these molecules and the fact that they are produced by living cells or organisms make it extremely difficult to predict whether the two biopharmaceuticals are indeed equivalent.
in terms of therapeutic efficacy and safety. To obtain authorization for marketing in the EU, the comparability of the biosimilar and reference drug must be demonstrated at both preclinical and clinical levels by means of a complex step-wise process. This also applies to changes in the manufacturing process used to produce the original biological agent.

Statement 1. Based on current evidence, two biosimilars that target the same molecule can be considered equivalent in terms of efficacy and safety only when such equivalence has been demonstrated in preclinical and clinical trials. [100%]

Statement 2. The objective of the initial phase of development and production of a biosimilar drug is not to establish patient benefit or therapeutic superiority relative to another biopharmaceutical: it is to provide clear demonstration that the new drug is equivalent to the reference product in terms of quality. Therefore, the clinical end points used in studies to obtain licensing of the biosimilar may differ from those used for registration of the reference products. However, adequately powered post-marketing clinical trials should be conducted to show/confirm the clinical equivalence of the two agents and to identify similarities and potential differences in their adverse event profiles [100%]

Statement 3. A biosimilar agent with proven efficacy and safety for one indication is not necessarily effective and safe for other indications. [95%]

Statement 4. It is highly recommended that, when the reference drug is used to treat IBD, evidence of the biosimilar’s efficacy and safety in this specific setting be obtained prior to marketing. [95%]

Statement 5. In any discussion of biologic therapy for IBD (with reference drugs or biosimilars), due consideration should be given to the markedly heterogeneous clinical presentation and course of these diseases and to the current absence of specific, clear-cut biomarkers that can be used to predict IBD patients’ responsiveness to these agents and to monitor their short-term efficacy (like haemoglobin level for epoetin therapy or glucose levels for insulin). [95%]

Statement 6. The regulatory rules and economic assumptions used for generic chemical medicines cannot be applied to biosimilars. Because of their lengthy development phase and complex production processes, the reduction in purchase price compared to the reference product is unlikely to be as substantial as for chemical generics. However, given the health-care system’s high yearly expenditures for reference biopharmaceuticals, the availability of biosimilars can be expected to result in a substantial absolute cost reduction. [100%]

Statement 7. An IBD patient being effectively controlled with an original biopharmaceutical should not be switched to a drug claimed to be that drug’s biosimilar until preliminary data supporting such changes have been reported. In addition, the change must be approved by the specialist prescribing the original biologic and be implemented after obtaining the patient’s written informed consent. [100%]

Statement 8. The IG-IBD favours the use of biosimilar agents, provided that they meet appropriate quality standards and that their safety and efficacy has been specifically verified in IBD patients. The Group also encourages the execution of clinical trials focused on biosimilars to further assess their efficacy and safety in IBD patients. [100%]

Statement 9. For biosimilars approved for use in IBD, post-marketing data specifically related to the biosimilar drug (as opposed to its reference product) must be acquired to: (a) detect less common but potentially harmful adverse effects, particularly those associated with long-term use; (b) monitor the actual frequency of expected adverse events. Assuming that the reduced cost of biosimilar therapy will have some impact on prescribing patterns, such data may also be useful for evaluating the effects of (for example) earlier access to treatment and the actual need for hospitalization and surgery. [100%]

5. Conclusion

The availability of biosimilars in IBD in the near future will be a challenge for physicians, patients, and third payers due to the complexity and heterogeneity of these diseases. Given the high yearly cost of therapy and the increasingly large number of patients in treatment, even a 25% reduction of the current market price represents a valuable opportunity for expanding access to therapy or modifying the distribution of health care costs. However, in the interest of patients and pharmaceutical companies alike, standards for safety and adequate testing must remain high, and no compromise can be accepted when prescribing the best treatment for each patient’s unique condition.

Conflict of interest

Vito Annese: Department of Medical and Surgical Specialties, Gastroenterology, AOU University Hospital Careggi, Florence, Italy. Speakers, consultant, advisory board or research grants from Giuliani, Abbvie, MS&D, Ferring, Takeda, Nycomed, Shire, Cosmo Pharmaceuticals, Sofar, SEDA, Hospira, Otsuka, Astra Zeneca, Dicofarm, Alfa Wassermann, Johnson & Johnson.

Maurizio Vecchi: University of Milan, Department of Biomedical Sciences for Health, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy. Speaker, consultant or advisory board member for Giuliani, Schering-Plough, Abbvie, MSD, Ferring, Takeda, Nycomed, Cosmo Pharmaceuticals, Sofar, Chiesi, Hospira, Otsuka.

Alessandro Armuzzi: IBD Unit, Columbus Clinic and Catholic University of Rome, Rome, Italy. Consultant for Abbvie, Hospira, Lilly, MSD, Sofar. Lecture fees/educational grants from Abbvie, Astra-Zeneca,Ferring, MSD, Otsuka, Takeda.

Livia Biancone: GI Unit, Department of Systems Medicine, University of Tor Vergata, Rome, Italy. Speaker or advisory board for: Schering-Plough, Abbvie, MSD, Wassermann, Zambon, Nycomed.

Fabrizio Bossa: Division of Gastroenterology, IRCCS-CSS Hospital, San Giovanni Rotondo, Italy. No conflict of interest.

Emma Calabrese: Gastroenterology Unit, Department of Systems Medicine, University of Rome Tor Vergata, Italy. Speaker grants for Abbvie, MSD.


Michele Comberlati: Division of Gastroenterology, Regional Hospital, Bolzano, Italy. Consultant and advisory board of MSD, Sofar and Abbvie.

Salvatore Cucchiara: Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Rome, Italy. Advisory Board Johnson and Johnson, International Registry of Biological Therapy for Pediatric IBD. Vedolizumab Pediatric Program Advisory Board Takeda.

Silvio Danese: IBD Center, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan, Italy. Speaker, consultant and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co., UCB Pharma, Ferring, Cellerix, Millennium Takeda, Nycomed, Pharmacosmos, Actelion, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson.

Marco Daperno: Gastroenterology Unit, AO Ordine Mauriziano, Torino Advisory boards of: Abbvie, MSD, Hospira, Takeda; he received grants for Lectures from: Chiesi, SOFAR, Ferring.

Renata D’Inca: Division of Gastroenterology, DISCoG, University of Padua, Italy. Advisory board of Abbvie, MSD, Hospira.

Gionata Fiorino: IBD Center, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan, Italy. Consultant and
a member of Advisory Boards for MSD, Takeda Pharmaceuticals, and Janssen Pharmaceuticals.

Walter Fries: Clinical Unit of Chronic Bowel Disorders, Dept. of Clinical and Experimental Medicine, University of Messina, Messina, Italy. Speaker Fees and Advisory Board AbbVie, Advisory Board MSD.

Paolo Gionchetti: IBD Unit, Dept of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. Speaker, consultant or advisory board member for AbbVie, MSD, Ferring, Takeda, Nymed, Sofar, Chiesi, Hospira.

Anna Kohn: Division of Gastroenterology, AO San Camillo Forlanini, Rome, Italy. No involvement with any financial or non-financial interest.

Giovanni Latella: Department of Life, Health and Environmental Sciences, Gastroenterology Unit, University of L’Aquila, L’Aquila, Italy. Consultant for MSD, Shire. Research grants from Giuliani, Alfa Wassermann, Sofar. Speaker’s fees from AbbVie Italy and Chiesi.

Gimmy Meucci: Unit of Gastroenterology and Endoscopy, San Giuseppe Hospital, Milan, Italy. No conflict of interest.

Ambrogio Orlando: Unit of Medicine 2°, A.O. “Villa Sofia-Cervello” Hospitals, Palermo, Italy. Advisory board of AbbVie, MSD, Hospira, Takeda. Lecture fees from: AbbVie, Chiesi, SOFAR, Ferring.

Claudio Papi: Gastroenterology and Hepatology Unit S Filippo Neri Hospital, Rome, Italy. Consultant for AbbVie. Educational grants from AbbVie, Chiesi and Sofar.

Beatrice Principi: Gastroenterology Unit (D.E.T.O.), University of Bari, Bari, Italy. Advisory Board for MSD&B, AbbVie, Takeda.

Antonio Rispo: Gastroenterology, Department of Clinical Medicine and Surgery, A.O.U. “Federico II” of Naples. Speaker, consultant or advisory board member for Schering-Plough, AbbVie, MSD, Ferring, Takeda, Chiesi, Zambon.

Fernando Rizzello: IBD Unit, Dept of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. Consultant for AbbVie, Takeda, MSD; lecture fees/educational grants from AbbVie, Chiesi and Sofar.

Simone Saibeni: Gastroenterology, Azienda Ospedaliera Guido Salvini, Hospital Rho, Milan, Italy. No conflict of interest.

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Appendix A. Collaborators

IG-IBD Governing Board:

Fabrizio Bossa, Division of Gastroenterology, IRCCS-CSS Hospital-San Giovanni Rotondo Italy.

Emma Calabrese, Gastroenterology Unit, Department of Systems Medicine, University of Rome Tor Vergata, Italy.

Marco Daperno, Gastroenterology Unit, AO Ordine Mauriziano, Torino, Italy.

Fernando Rizzello, IBD Unit, Dept of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. Antonio Rispo, Gastroenterology, Department of Clinical Medicine and Surgery, A.O.U. “Federico II” of Naples, Italy.

Simone Saibeni, Gastroenterology, Azienda Ospedaliera Guido Salvini, Hospital Rho, Milan, Italy.

IG-IBD members:

Alessandro Armuzzi, IBD Unit, Columbus Clinic and Catholic University of Rome, Rome, Italy.

Livia Biancone GI Unit, Department of Systems Medicine, University of Tor Vergata, Rome, Italy.

Fabiana Castiglione, Gastroenterology, Department of Clinical Medicine and Surgery, A.O.U. “Federico II” of Naples, Italy.

Michele Commelini, Division of Gastroenterology, Regional Hospital, Bolzano, Italy.

Salvatore Cucchiara, Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Rome, Italy.

Silvio Danese, IBD Center, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan, Italy.

Renata D’Incà, Division of Gastroenterology, DISCoG, University of Padua, Italy.

Gionata Fiorino, IBD Center, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan, Italy.

Walter Fries, Clinical Unit of Chronic Bowel Disorders, Dept. of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

Paolo Gionchetti, IBD Unit, Dept. of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. Anna Kohn, Division of Gastroenterology, AO San Camillo Forlanini, Rome, Italy.

Giovanni Latella, Department of Life, Health and Environmental Sciences, Gastroenterology Unit, University of L’Aquila, L’Aquila, Italy. Giovanna Sanfilippo, Consultant San Medice, Hospita.

Marco Simone, Simona Saibeni, Consultant San Medice, Hospita.

Fernando Orlando, Unit of Medicine 2°, A.O. “Villa Sofia-Cervello” Hospitals, Palermo, Italy.

Claudio Papi, Gastroenterology and Hepatology Unit S Filippo Neri Hospital, Rome, Italy. Beatrice Principi, Gastroenterology Unit (D.E.T.O.), University of Bari, Bari, Italy.

Beatrice Principi, Gastroenterology Unit (D.E.T.O.), University of Bari, Bari, Italy.

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