Digestive and Liver Disease 51 (2019) 724–729

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Epidemiology of primary biliary cholangitis in Italy: Evidence from a real-world database

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ARTICLE INFO

Article history:
Received 11 July 2018
Received in revised form 5 November 2018
Accepted 9 November 2018
Available online 17 November 2018

Keywords:
Obeticholic acid
Ursodeoxycholic acid

ABSTRACT

Background: Primary biliary cholangitis is an autoimmune disease affecting the interlobular bile ducts. Limited information is available on its epidemiology and treatment in Italy.
Aims: To describe primary biliary cholangitis epidemiology and investigate treatment patterns for Italian patients with this disease.
Methods: Electronic medical records from 900 general practitioners (part of the QuintilesIMS™ Longitudinal Patient Databases) were examined. Demographics were compared with those from the Italian National Institute of Statistics dataset. The *International Classification of Diseases, Ninth Revision*, biliary cirrhosis code 571.6 was used for diagnosis, and data on comorbidities, concomitant medications, medical examinations, specialist referrals, and treatments were collected.
Results: This dataset was representative of the Italian population. Point prevalence of primary biliary cholangitis was calculated as 27.90 per 100,000 and incidence as 5.31 per 100,000 inhabitants/year. Some associations between the disease and comorbidities were sex specific. The most common laboratory assays requested were for liver enzymes, and the majority of patients were not referred to a specialist. Ursodeoxycholic acid was the most common therapy.
Conclusion: This can be used as a benchmark for monitoring and identifying unmet needs to improve treatment in Italy.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease with susceptibility modulated by genetics and environmental exposures [1–3]. The disease is typically characterized by loss of immune tolerance for a mitochondrial antigen with damage specific to the biliary epithelium [1,4,5]. Immune responses to interlobular bile ducts cause chronic inflammation that can lead to cholestasis and liver cell injury [1,2].

The majority of patients with PBC are asymptomatic at diagnosis, but 51% become symptomatic by 5 years, and 95% are symptomatic after 20 years [6,7]. Classic symptoms of PBC include fatigue and pruritus [1,8]. The disease is also associated with other autoimmune disorders and can cause hyperlipidemia, metabolic bone disease, and vitamin deficiencies [1,9–11]. Global therapeutic approaches for PBC are still limited; approved treatments include ursodeoxycholic acid (UDCA) as first-line therapy and obeticholic acid for second-line therapy in patients with inadequate response or intolerance to UDCA; off-label medications include fibric acid derivatives and budesonide [5,12,13]. No currently available therapy targets the etiology of PBC or cures the disease [14].

A systematic review of studies in Europe, North America, Asia, and Australia reported incidence rates of PBC ranging from 0.33 to 5.8 per 100,000 inhabitants/year and prevalence rates ranging from 1.91 to 40.2 per 100,000 inhabitants [15]. In a 2017 Orphanet systematic review of worldwide registries, health institutes and agencies, and published literature, incidence of PBC was estimated as 3 per 100,000 and prevalence as 21.05 per 100,000 [16]. In 5

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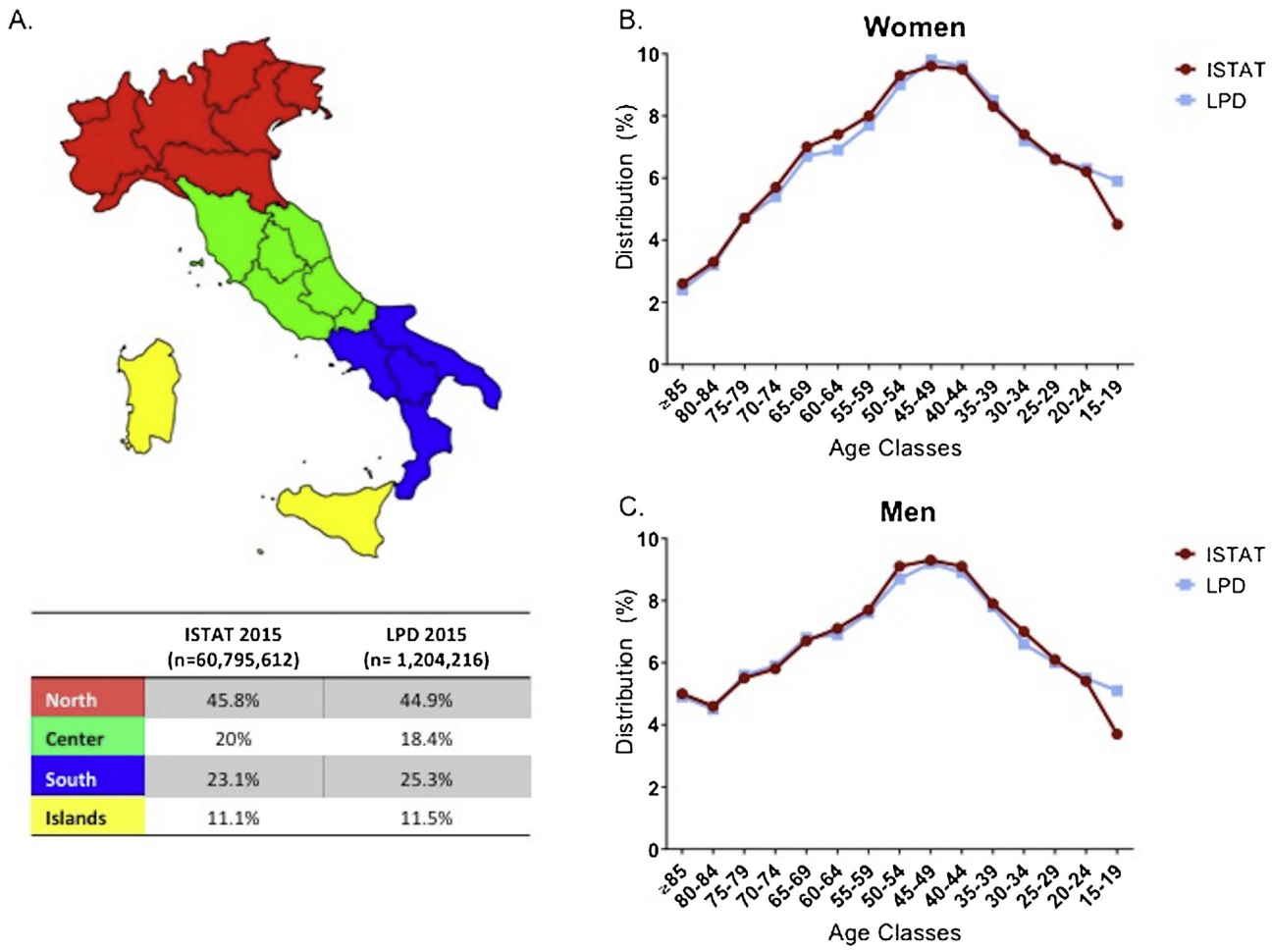
https://doi.org/10.1016/j.dld.2018.11.008



	ISTAT 2015 (n=60,795,612)	LPD 2015 (n= 1,204,216)
North	45.8%	44.9%
Center	20%	18.4%
South	23.1%	25.3%
Islands	11.1%	11.5%

Fig. 1. Comparison of demographic information between Italian National Institute of Statistics dataset and Longitudinal Patient Databases [22]. A: Map of regions in Italy and corresponding population in each database. B-C: Comparison of distributions across age classes in women (B) and men (C) between databases. Abbreviations: ISTAT, Italian National Institute of Statistics; LPD, Longitudinal Patient Databases.

years (2004–2009) of administrative database records from Lombardy, Italy, an incidence of 1.67 per 100,000 was observed [17]. In the same study, an analysis of point prevalence that included diagnoses from hospital records resulted in an estimate of 16.0 per 100,000 in 2009 [17]. A revised analysis that also included patients who used a disease-related exemption code that enabled them to avoid co-payment for medical visits and procedures increased the point prevalence estimate to 29.5 per 100,000 in 2010 [17]. A retrospective-prospective PBC registry including ~50 centers in Italy was enrolling at the time of this publication; however, results are not currently available. The aim of the current study was to investigate PBC epidemiology in Italy and link it to treatment patterns for Italian patients with PBC.

2. Materials and methods

The information contained in the database used in this study was recorded by general practitioners in their clinical practice. Data from electronic medical records of patients from 900 general practitioners in Italy were obtained from the QuintilesIMS™ Longitudinal Patient Databases (LPD®). This is a proprietary dataset of patient and prescription information collected by the QuintilesIMS company, now rebranded as IQVIA [18]. The database from this company is also the basis for the Medicines Utilisation Monitoring Center (OsMed) report published annually by AIFA, the Italian Medicines Agency [19].

To validate that the LPD population was representative of the entire Italian population, characteristics of patients in the study were compared with those reported in the most recent Italian National Institute of Statistics (ISTAT) data, which include Italian census information. Diagnosis of PBC was based on use of the biliary cirrhosis code (*International Classification of Diseases, Ninth Revision* [*ICD-9*]: 571.6) from January 2014 to December 2015. Evaluation of prevalence and incidence was performed on individuals with PBC in 2015, to obtain the most recent yearly estimates available in the dataset. Although the 571.6 code may be applied to multiple conditions (eg, PBC, secondary sclerosing cholangitis, and other potentially incorrect designations [20]), it was considered a proxy for PBC given the low prevalence of other diseases that may be assigned the 571.6 code.

Incidence was defined as no mention of PBC disease in a patient's medical records within 12 months before the first report in the 2-year period of observation. Treatment information was collected at the first diagnosis of PBC, and data on demographics and comorbidities were collected up to a year before diagnosis (preselection period). The follow-up period was 6 months after diagnosis, during which information on concomitant medications, specialist referrals, and medical examinations (eg, biochemical examinations, imaging findings) was collected.

Statistical analyses involved Student *t* tests to evaluate differences between the means (± standard deviation) of groups. Percentages were compared between groups with a chi-square test.

Table 1
Demographic information for the complete Longitudinal Patient Databases population and patients with primary biliary cholangitis.

	LPD population (N = 1,204,216)	LPD PBC population (N = 412)	*p*-Value
Age, y (Mean ± SD)	52.8 ± 20.3	64.7 ± 14.4	<0.001
Sex (% Female/% Male)	54/46	82/18	<0.001
BMI, kg/m^2 (Mean ± SD)	26 ± 5.3	26 ± 4.6	Not significant

Abbreviations: BMI, body mass index; LPD, Longitudinal Patient Databases; PBC, primary biliary cholangitis; SD, standard deviation.

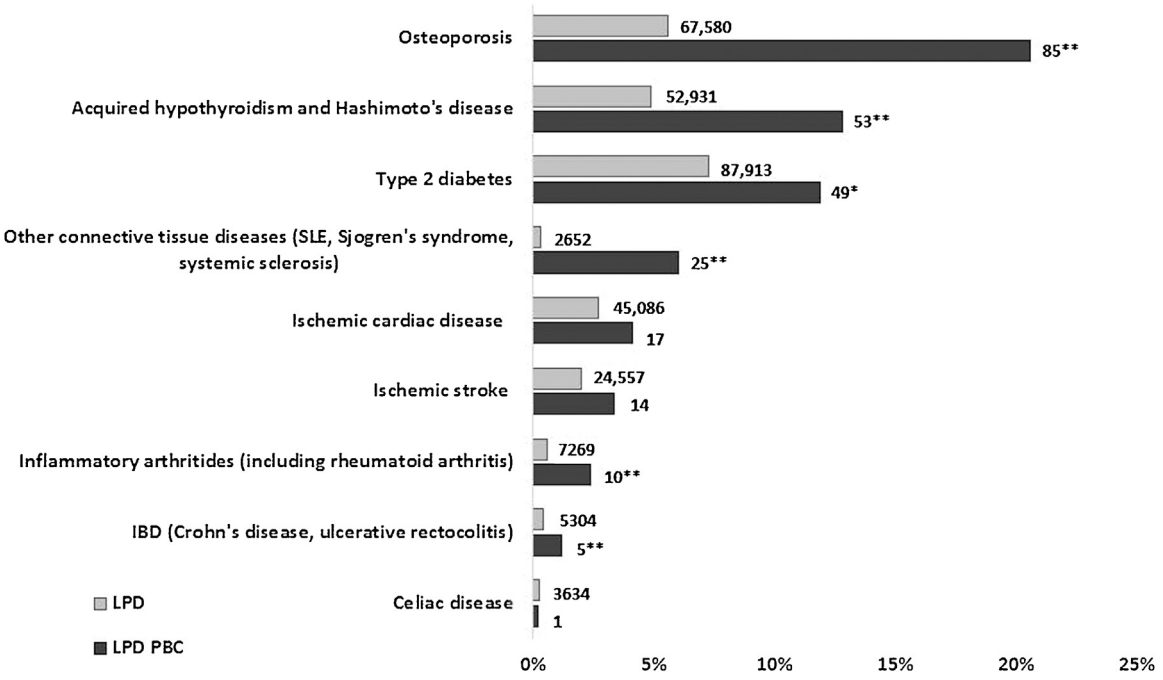


Fig. 2. Comorbidities in the general database population versus in the subset diagnosed with primary biliary cholangitis. *$p < 0.05$; **$p < 0.01$. Absolute numbers of patients affected are reported at the end of each histogram bar. In the Longitudinal Patient Databases population, the total number of patients was 1,204,216; in the subset with primary biliary cholangitis, 412. Abbreviations: LPD, Longitudinal Patient Databases; PBC, primary biliary cholangitis; SLE, systemic lupus erythematosus.

PASS 2008 and NCSS 2007/GESS 2006 statistical software were used in the analyses.

3. Results

3.1. Demographics

In total, 1,204,216 inhabitants >14 years old were analyzed from the LPD data. This dataset contained ~2% of Italian residents, and the distribution of individuals was validated to be representative of the general Italian population (per ISTAT data [21]) with respect to geographical distribution, sex, and age (Fig. 1) [22]. The subset of patients with PBC in the LPD data were on average older and included a higher proportion of female patients than the whole LPD population (Table 1). There were no significant differences in body mass index between patients with PBC and the general LPD population.

3.2. Prevalence and incidence of primary biliary cholangitis in Italy

The number of patients with a diagnosis of PBC in 2014–2015 was 412. In 2015, 336 patients were recorded, of whom 64 were newly diagnosed. The number of patients diagnosed in 2014 did not significantly differ from the number diagnosed in 2015: 357 patients were recorded, of whom 79 (22%) were newly diagnosed. Of those identified in 2014, 272 were also recorded in 2015, whereas 85 were lost to follow-up. Of these 85 patients, 9 died and 1 changed general practitioners. Point prevalence of PBC was calculated as 27.90 per 100,000 inhabitants and incidence of PBC as 5.31 per 100,000 inhabitants/year.

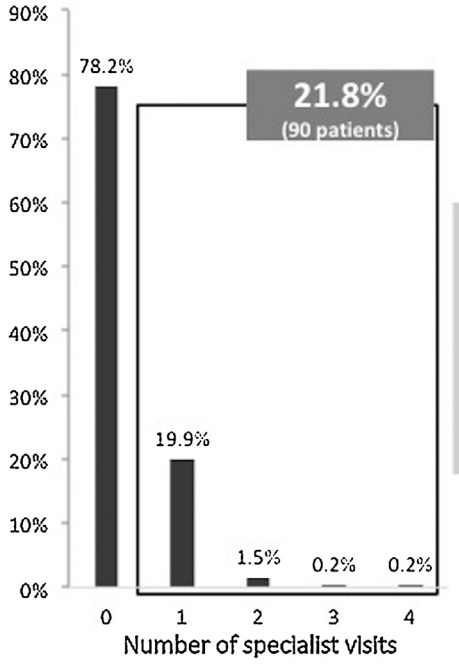
3.3. Comorbidities

Comorbidities that were significantly ($p < 0.05$) more common in the LPD PBC population than in the general LPD population were osteoporosis, inflammatory arthritides [including rheumatoid arthritis, other connective tissue diseases (specifically, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis), inflammatory bowel disease (IBD; ie, Crohn's disease, ulcerative rectocolitis), type 2 diabetes, and acquired hypothyroidism/Hashimoto's disease] (Fig. 2).

Patterns of comorbidities were also assessed by sex. In both women and men, type 2 diabetes and acquired hypothyroidism/Hashimoto's disease were significantly ($p < 0.01$) more prevalent in the LPD PBC population than in the general LPD population. In women, osteoporosis, inflammatory arthritides, and other connective tissue diseases were significantly ($p < 0.01$) more common in the LPD PBC population than in the general LPD population; these findings were not observed in men. The only male-specific enrichment in the LPD PBC population versus the general LPD population was IBD ($p < 0.01$).

3.4. Laboratory assays and imaging findings

During the 6-month study period, general practitioners requested ≥1 assay in most patients with a PBC diagnosis (ie,



Specialist visit	Patients with specialist visit (n= 90)	%	Total number of visits	Mean number per patient
Hepatologist	38	42.2	48	1.3
Gastroenterologist	33	36.7	47	1.4
Internist	12	13.3	18	1.5
Infectious Disease Specialist	4	4.4	4	1.0
Reumatologist	4	4.4	6	1.5
Dietician	2	2.2	2	1.0
Dermatologist	1	1.1	1	1.0
Neurologist	1	1.1	1	1.0
Hematologist	1	1.1	1	1.0
Geriatrics	1	1.1	1	1.0
Pain Specialist	1	1.1	2	2.0
Home Visit	1	1.1	1	1.0
Surgeon	1	1.1	1	1.0
Ophthalmologist	1	1.1	1	1.0

Fig. 3. Specialist referrals related to primary biliary cholangitis diagnosis requested by general practitioners.

both prevalent and incident cases). The most common laboratory assays measured liver enzyme levels: alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, and alkaline phosphatase; serum bilirubin was also frequently measured. In addition, a complete blood count was requested for most patients. Clinicians did not commonly request imaging in patients with PBC; therefore, no summary or inferences about these data are provided.

3.5. Treatments

In 88.4% of patients, at least 1 medication was prescribed for the treatment of PBC; among these patients, 91.8% were treated with UDCA. Of those prescribed UDCA, only 22.8% received additional PBC drugs. The number of incident patients (ie, diagnosed in 2014 or 2015) treated for PBC was lower than the number of previously diagnosed patients (76.1% versus 88.4%, $p < 0.001$). The majority of patients with PBC received ≥1 concomitant medication prescribed for a diagnosis other than PBC. Among patients prescribed concomitant medications, the most common were those for gastroesophageal reflux disease, systemic antibacterials, and agents acting on the renin-angiotensin-aldosterone system.

3.6. Specialist referrals

The majority of patients with PBC were not referred to a specialist during the study period (Fig. 3). Patients were most commonly referred to hepatologists. General practitioners also referred patients with PBC to gastroenterologists, internists, and other specialists.

4. Discussion

The point prevalence (27.90/100,000) and incidence (5.31/100,000/year) of PBC estimated in this Italian study are within the range reported in a global systematic review (prevalence, 1.91–40.2/100,000; incidence, 0.33–5.8/100,000/year) [15]. The point prevalence of PBC in this study is also very close to that calculated in the Italian region of Lombardy when both exemption code registry and inpatient registry (29.5/100,000) are considered [17]. However, our definition of incidence involved no mention of PBC disease in patient medical records within only 12 months before the observation period, which differs from the methodology of other studies and makes direct comparisons of results challenging. In the previous Italian study, incidence was defined as the number of patients with a first-time diagnosis of PBC in a year divided by the total number of inhabitants at the beginning of the year [17], and global estimates [15,16] were obtained from multiple sources most likely with varying definitions.

The prevalence and incidence of PBC may be overestimated by 10%–15% in this study because of the timeframe used to define incidence and other forms of cholangitis that could be associated with the biliary cirrhosis/cholangitis code (*ICD*-9: 571.6), including primary sclerosing cholangitis (PSC) or secondary cirrhosis. The values of prevalence and incidence would also be overestimated if the LPD population was not a random sample but rather a population actively seeking healthcare. In contrast, considering that PBC is often asymptomatic, particularly in the early stages, the disease may have gone undiagnosed or been misdiagnosed in some patients; this would result in underestimation of its prevalence and incidence. Although these possibilities cannot be excluded, demographic information from the study suggests it was representative of the Italian population. From our data on prevalence and considering that ~15% of patients with the *ICD-9* 571.6 code were assigned a diagnosis other than PBC, we estimate a total number of ~13,000 to ~14,000 PBC cases in Italy in 2015.

The total number of patients identified with PBC and those reported as having the disease in 2015 differ by 85 patients. These patients were "lost" to general practitioner follow-up in 2015; a small proportion may be due to death or to switching general practitioners. Some of the "lost" patients may have been examined

and prescribed medication by a hepatologist or other specialist; however, specialist records were not available for confirmation. A referral from a general practitioner was not mandatory for patients to access specialty physicians.

The most common comorbidities in this study were osteoporosis, hypothyroidism, and diabetes, which have important implications for treatment of patients with PBC. These results agree with previous reports of a higher prevalence of osteoporosis (from a case-control study in Morocco) [23] and autoimmune thyroid disease (from an interview-based study in the United States) [24] in patients with PBC than in controls. Diabetes mellitus (not specifically type 2) showed similar prevalence in patients with PBC and in controls in the US cohort [24], which may be attributable to the inclusive disease definition in the US study and the high baseline disease prevalence in the United States. Some comorbidities, including osteoporosis, may have been more common in the PBC populations because of disease effects or because they were confounded by age and sex distribution, by comorbidities associated with osteoporosis, or by treatment for those comorbidities.

In the current study, IBD was associated with PBC in men but not women; osteoporosis, inflammatory arthritides, and other connective tissue diseases were associated with PBC in women but not men. Because PSC is associated with IBD and male sex [15], the association of IBD with PBC in men could be due in part to misclassification of PSC patients in this PBC cohort. The sex difference for osteoporosis was observed in patients with chronic liver disease (including PBC) in a case-control study [23]. The sex-specific pattern for inflammatory arthritides and other connective tissue diseases is consistent with significant associations between female sex and autoimmune disorders in an Italian cohort study [25] and in a cross-sectional Japanese study [26].

Consistent with standard-of-care guidelines [5], UDCA was the most common therapy for PBC in this study. The observed percentage of all patients with PBC receiving UDCA (81%) is similar to that recently reported in international (85%–90%) [27,28] and US (70%) [29] cohort studies. The estimation of patients receiving monotherapy and concomitant medication relies on physicians accurately indicating which drugs are intended for the treatment of PBC with disease codes, and general practitioners might assign incorrect codes to save time.

Additional medications that have been used off-label as second-line or adjunctive therapy for PBC include fibric acid derivatives and budesonide, a corticosteroid [5]. These medications were not reported as common PBC treatments in this study; fibrates were prescribed for another diagnosis in 1.7% of the overall PBC LPD population, systemic corticosteroids in 12.9%, and budesonide in 0.2%. It is not clear whether these medications were strictly intended to treat a non-PBC diagnosis or if they were also intended for the off-label treatment of PBC.

During the study, 21.8% of patients were referred to a specialist. Not surprisingly, hepatologists were the most commonly visited specialist. Laboratory assays examining liver enzymes were often requested in patients with PBC, as is expected for a liver disorder. As a caveat, not all the tests performed in patients who visit a specialist would be included in these data, which were collected from general practitioners. In addition, we considered visits and prescribed tests within 6 months of the first 571.6 code. This could result in an underestimation of specialist visits requested by the healthcare provider.

The database we used includes general practitioners from all the regions in Italy, offering a wider picture of the epidemiology of this disease compared with previous studies. Our database also offers some information beyond the epidemiological data: It gives the chance to investigate the management of these patients regarding general practitioner's practice, with an emphasis on treatment, appropriateness of laboratory tests, and the requirement of specialist visits.

In summary, we evaluated the prevalence and incidence of PBC in Italy and described the typical features of its management. Data collected provide unique and valuable insights into the current epidemiology of PBC in Italy, key characteristics of patients with PBC, and treatment patterns. This information can be used as a benchmark for monitoring trends over time and identifying unmet needs to improve management as well as access to and flow of care.

Conflicts of interest

For authors of "Epidemiology of Primary Biliary Cholangitis in Italy: Evidence From a Real-world Database": Marco Marzioni, MD, has no conflicts of interest. Chiara Bassanelli, MD, PhD, is an employee of Intercept Italia srl. Claudio Ripellino and Duccio Urbinati, PharmD, are employees of IMS Health. Domenico Alvaro, MD, has received research grants from and has served as a speaker and consultant for Intercept Pharmaceuticals.

Funding

Technical and editorial support for this manuscript was provided by MedLogix Communications, LLC, and funded by Intercept, which also funded IMS data analysis. The authors did not receive an honorarium to participate.

Acknowledgments

Technical and editorial support for this manuscript was provided by Carolyn Green, PhD, of MedLogix Communications, LLC, and funded by Intercept. The authors thank Barbara Marini, PhD, Intercept Italia srl, for her contribution.

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