

Biological therapy in inflammatory bowel diseases: Access in Central and Eastern Europe

Fanni Rencz, Márta Péntek, Martin Bortlik, Edyta Zagorowicz, Tibor Hlavaty, Andrzej Śliwczyński, Mihai M Diculescu, Limas Kupcinskas, Krisztina B Gecse, László Gulácsi, Peter L Lakatos

Fanni Rencz, Márta Péntek, László Gulácsi, Department of Health Economics, Corvinus University of Budapest, H-1093 Budapest, Hungary

Fanni Rencz, Semmelweis University Doctoral School of Clinical Medicine, H-1085 Budapest, Hungary

Martin Bortlik, IBD Clinical and Research Centre, ISCARE a.s., 1st Faculty of Medicine, Charles University, 170004 Prague, Czech Republic

Edyta Zagorowicz, Department of Gastroenterology, The Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology and Medical Center for Postgraduate Education, 01-813 Warsaw, Poland

Tibor Hlavaty, Gastroenterology Unit, Department of Internal Medicine V, University Hospital Bratislava, SK-82606 Bratislava, Slovakia

Andrzej Śliwczyński, Public Health Department, Health Sciences Faculty, Medical University in Łódź and National Health Fund, 02-390 Warsaw, Poland

Mihai M Diculescu, Department of Gastroenterology and Hepatology, Carol Davila University, 020022 Bucharest, Romania

Limas Kupcinskas, Department of Gastroenterology, Medical Academy, Lithuanian University of Health Sciences, 50009 Kaunas, Lithuania

Krisztina B Gecse, Péter L Lakatos, 1st Department of Medicine, Semmelweis University, H-1083 Budapest, Hungary

Author contributions: Gulácsi L and Lakatos PL equally contributed to the paper and were involved in all activities including the design, epidemiology and antTNF access data collection, data analysis and drafting and revising the manuscript; Rencz F and Péntek M were involved in data analysis and drafting and revising the manuscript; all other authors were involved in drafting and revising the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Péter L Lakatos, MD, DSc, PhD, 1st Department of Medicine, Semmelweis University, Korányi S. 2/A, H-1083 Budapest,

Hungary. lakatos.peter_laszlo@med.semmelweis-univ.hu

Telephone: +36-1-2100278

Fax: +36-1-310250

Received: September 3, 2014

Peer-review started: September 4, 2014

First decision: October 14, 2014

Revised: October 24, 2014

Accepted: December 1, 2014

Article in press: December 1, 2014

Published online: February 14, 2015

Abstract

Biological drugs opened up new horizons in the management of inflammatory bowel diseases (IBD). This study focuses on access to biological therapy in IBD patients across 9 selected Central and Eastern European (CEE) countries, namely Bulgaria, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania and Slovakia. Literature data on the epidemiology and disease burden of IBD in CEE countries was systematically reviewed. Moreover, we provide an estimation on prevalence of IBD as well as biological treatment rates. In all countries with the exception of Romania, lower biological treatment rates were observed in ulcerative colitis (UC) compared to Crohn's disease despite the higher prevalence of UC. Great heterogeneity (up to 96-fold) was found in access to biologicals across the CEE countries. Poland, Bulgaria, Romania and the Baltic States are lagging behind Hungary, Slovakia and the Czech Republic in their access to biologicals. Variations of reimbursement policy may be one of the factors explaining the differences to a certain extent in Bulgaria, Latvia, Lithuania, and Poland, but association with other possible determinants (differences in prevalence and incidence, price of biologicals, total expenditure on health, geographical access, and cost-effectiveness results) was not proven. We assume, nevertheless, that health

deterioration linked to IBD might be valued differently against other systemic inflammatory conditions in distinct countries and which may contribute to the immense diversity in the utilization of biological drugs for IBD. In conclusion, access to biologicals varies widely among CEE countries and this difference cannot be explained by epidemiological factors, drug prices or total health expenditure. Changes in reimbursement policy could contribute to better access to biologicals in some countries.

Key words: Inflammatory bowel diseases; Ulcerative colitis; Biological therapy; Access; Europe, Central and Eastern; Crohn's disease

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Great heterogeneity ranging up to 96-fold difference in access of inflammatory bowel diseases (IBD) patients to biologicals can be found across Central and Eastern Europe (CEE): Poland, Bulgaria, Romania, and the Baltic States have, to date, fallen behind Hungary, Slovakia and the Czech Republic. The following factors did not explain the considerable variations among the CEE countries: differences in prevalence and incidence, price of biologicals, total expenditure on health, geographical access, clinical guidelines, and cost-effectiveness results. We assume that health deterioration linked to IBD might be valued differently against other systemic inflammatory conditions in distinct countries which contributes to the great heterogeneity.

Rencz F, Péntek M, Bortlik M, Zagorowicz E, Hlavaty T, Śliweczyński A, Diculescu MM, Kupcinskas L, Geese KB, Gulácsi L, Lakatos PL. Biological therapy in inflammatory bowel diseases: access in Central and Eastern Europe. *World J Gastroenterol* 2015; 21(6): 1728-1737 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i6/1728.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i6.1728>

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic, chronic inflammatory disorders of the gastrointestinal tract known as inflammatory bowel diseases (IBD). In general, IBD is characterised by flare-ups and remissions of varying duration and severity, and only a minority of patients experience a chronic, continuous disease course^[1]. CD may involve any part of the digestive tract, but mainly affects the distal ileum and the colon, whereas UC usually starts in the rectum and extends in a continuous retrograde manner through part of, or the entire colon^[1,2]. Approximately 80% of CD patients will require at least one intestinal surgery, while 10%-30% of UC patients will undergo colectomy during their lifetime^[1]. Due to

early onset, fluctuating disease course, unpredictable prognosis and lack of a cure, IBD poses a considerable burden on patients.

Introduction of biological drugs in the treatment of IBD has brought a paradigm shift in patient management and treatment goals that promoted corticosteroid-free clinical, endoscopic, and biomarker remission^[3,4]. Infliximab was the first biological approved by European Medicines Agency (EMA) for treatment of CD in 1999, then 7 years later in UC, adalimumab was registered in 2007 in CD and 5 years later in UC. Furthermore, golimumab received authorisation for the treatment of UC in 2013. Although biologicals have been marketed in Western Europe for over 15 years now, the access is fairly difficult in certain CEE countries. Of note, in 2013, biosimilar infliximab has been approved for the same indications as the original drug and has now been marketed first in the CEE region^[5], and may affect the access to biologicals worldwide as well as in the CEE countries.

This study aimed to explore access to biological therapy of IBD patients in nine Central and Eastern European (CEE) countries, namely Bulgaria, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania and Slovakia. Literature data was systematically reviewed on the epidemiology and disease burden of IBD in these CEE countries. We also aimed to explore whether the access to biologicals is different in these countries and furthermore, to identify possible factors that predispose to regional differences.

EPIDEMIOLOGY

Recent data indicate that the incidence and prevalence of IBD are increasing over time and in different geographical locations^[6]. In Europe, the annual incidence of CD and UC ranges between 0.3-12.7 and 0.6-24.3 per 100000 person-years, respectively^[6]. European prevalence rates vary between 4.9-505 per 100000 persons for UC and 0.6-322 per 100000 persons in CD^[6]. The peak ages for CD and UC occurrence are 20-30 years and 30-40 years, respectively; and paediatric IBD accounts for 7%-20% of all cases^[1].

To provide an insight into the epidemiology of IBD in the CEE countries, we relied on the summary introduced by Lakatos *et al*^[7] in 2006, and incorporated results of a complementary systematic literature search for the period between 2006 and June 30th, 2014. We included publications that dealt with the 9 selected CEE countries, and excluded those that investigated only paediatric IBD (Table 1).

Overall 17 studies from 7 CEE countries were identified with observation periods varying from 1951 to 2013. No data was available on the epidemiology of IBD from Bulgaria or Latvia. To date, only one multi-country study has been carried out that involved 5 out of the 9 countries of interest^[8]. Among CEE countries, the highest incidence and prevalence rates were noted

Table 1 Incidence and prevalence of Crohn's disease and ulcerative colitis in the total population in 9 selected Central and Eastern European countries

Ref.	Country, region/city	Study period	Incidence/10 ⁵		Prevalence/10 ⁵	
			CD	UC	CD	UC
Burisch <i>et al</i> ^[8] , 2014 ¹	Czech Republic, Prague	2010	5.50	5.5	-	-
	South Bohemia		3.80	3.8		
Bitter and Hulec ^[45] , 1980	Czech Republic, North Bohemia	1968-1978	-	1.3	-	17.6
Nedbal <i>et al</i> ^[46] , 1967	Czech Republic	1960-1965	-	1.4	-	10.7
Salupere ^[47] , 2001	Estonia, Tartu County	1993-1998	1.40	1.7	-	-
Kull <i>et al</i> ^[48] , 1998	Estonia, Tartu County	1973-1992	0.27	1.5	-	-
Burisch <i>et al</i> ^[8] , 2014 ¹	Estonia, Southern Estonia	2010	5.20	5.2	-	-
Nagy <i>et al</i> ^[49] , 2004	Hungary, Borsod-Abaúj-Zemplén County	1962-1992	-	1.4	-	10.4
Lakatos <i>et al</i> ^[10] , 2011	Hungary, Western Hungary	2002-2006	8.87	11.9	115.3	211.1
Lakatos <i>et al</i> ^[9] , 2004	Hungary, Veszprém County	I: 1997-2001 P: 1991-2001	2.23	5.89	52.9	142.6
Burisch <i>et al</i> ^[8] , 2014 ¹	Hungary, Veszprém County	2010	11.5	10.3	-	-
Zvirbliene <i>et al</i> ^[50] , 2003 ²	Lithuania	1995-2001	-	-	10.0	30-40
Kiudelis <i>et al</i> ^[51] , 2012	Lithuania, Kaunas	2007-2009	1.21	6.56	-	-
Burisch <i>et al</i> ^[8] , 2014 ¹	Lithuania, Kaunas	2010	2.40	6.1	-	-
Chojacki ^[52] , 1964	Poland, Warsaw	1951-1960	0.66	-	66.0	-
Wiercinska-Drapalo <i>et al</i> ^[53] , 2005	Poland, Bialystok	1990-2003	0.10	1.8	-	-
Gheorghe <i>et al</i> ^[54] , 1997	Romania, Bucharest	1990-1997	0.42	-	-	-
Gheorghe <i>et al</i> ^[11] , 2004	Romania, nationwide	I: 2002-2003 P: 2004	0.50	0.97	1.51	2.42
Toader ^[55] , 2008	Romania, North-East region	1988-2007	1.54	0.35	-	-
Burisch <i>et al</i> ^[8] , 2014 ¹	Romania, Timis	2010	1.70	2.4	-	-
Prikazská <i>et al</i> ^[56] , 1996	Slovakia, nationwide	1994	6.75	-	-	-
Prikazka <i>et al</i> ^[57] , 1998	Slovakia, nationwide	1994	-	-	6.75	-
Gregus <i>et al</i> ^[12] , 2014	Slovakia	2013	4.60	6.8	80.5	150.5

¹Aged ≥ 15 years; ²Extrapolation by Lakatos *et al*^[7], 2006. I: Incidence; P: Prevalence; CD: Crohn's disease; UC: Ulcerative colitis.

Table 2 Estimated number of newly diagnosed and prevalent Crohn's disease and ulcerative colitis patients aged ≥ 15 years in 9 selected Central and Eastern European countries, 2013

	Number of new patients			Total patient number		
	CD	UC	Total	CD	UC	Total
Bulgaria	208	290	497	6162	11381	17543
Czech Republic	416	416	833	8768	16192	24960
Estonia	58	58	116	1090	2013	3103
Hungary	975	873	1848	9775	17897	27672
Latvia	57	80	137	1695	3131	4826
Lithuania	61	155	216	2482	4584	7066
Poland	1080	1506	2586	32049	59188	91237
Romania	287	405	692	16526	30520	47046
Slovakia	211	311	522	3687	6893	10580
Total	3353	4094	7447	82235	151798	234033

Data sources: Numbers of new patients were estimated based on incidence data by Burisch *et al*^[8], 2014. In case of the Czech Republic mean of two available regional incidence data was calculated (4.65/10⁵ both for CD and UC), and for Bulgaria and Lithuania mean incidence rate of 8 CEE countries (Croatia, Czech Republic, Estonia, Hungary, Lithuania, Moldova, Romania, and Russia) calculated by Burisch *et al*^[8] was applied (CD 3.3/10⁵, UC 4.6/10⁵). Total patient number was estimated using data from Gregus *et al*^[12], 2014 for Slovakia (CD 80.5/10⁵, UC 150.5/10⁵) and Lakatos *et al*^[10], 2011 for Hungary (CD 115.3/10⁵, UC 211.1/10⁵). For the other countries mean prevalence rates of Slovakia and Hungary were applied (CD 97.9/10⁵, UC 180.8/10⁵). Population data were obtained from Eurostat Statistics Database^[34]. CD: Crohn's disease; UC: Ulcerative colitis.

in Hungary (incidence CD 8.87/10⁵, UC 11.9/10⁵ and prevalence CD 115.3/10⁵, UC 211.1/10⁵), while the

lowest in Romania (incidence CD 0.5/10⁵, UC 0.97/10⁵ and prevalence CD 1.51/10⁵, UC 2.42/10⁵)^[9-11]. Nevertheless, comparison of these studies is hampered by the different study designs, investigation periods, length of follow-up, country regions, genetic and lifestyle characteristics, and age-groups included.

CEE was previously seen as a low incidence area. Nonetheless, more recent data has confirmed increasing incidence and prevalence trends. For instance, latest studies highlighted that incidence and prevalence in certain CEE countries, *e.g.*, the Czech Republic, Estonia, Hungary, and Slovakia emerging to that observed in Western and Northern European countries^[8,10,12].

The estimated number of patients annually diagnosed with IBD (aged ≥ 15 years) approached 7500 (55% UC) within the region. Our findings suggest that in 2013, there were approximately 235000 IBD patients (aged ≥ 15 years) between these countries and the proportion of patients with UC added up to 65% (Table 2). Of note, these patient numbers are extrapolations based on available epidemiology data.

DISEASE BURDEN

IBD is a disabling condition that considerably reduces patients' health-related quality of life and influences their professional, social and personal lifestyle^[13]. Due to the early onset and chronic character of the disease, patients have to deal with their disorder throughout their lifetime. The overall mortality of IBD

patients is slightly, but significantly higher than in the general population with standardized mortality ratios of 1.39 for CD and 1.19 for UC, respectively^[14,15].

In Western countries, IBD is associated with an excessive economic burden. In 2006, the average direct medical costs of CD amounted to €2898-6960/patient/year in Western Europe^[16]. Mean annual per patient direct medical costs of UC ranged from €8949 to €10395, and total economic burden of UC accounted for €12.5-29.1 billion annually in Europe (2008 prices)^[17]. Earlier studies from the past decade pointed out that primary cost drivers of IBD were surgical treatments and hospitalizations^[18,19]. Nevertheless, recent studies indicated that healthcare costs of IBD have shifted from hospitalization and surgery towards drug therapy, mainly due to the increasing use of biological drugs^[20,21]. Besides medical costs, a substantial proportion of patients are young adults and thus, indirect costs related to productivity loss at work account for about 16%-69% of the total burden^[17,19-21].

Limited data are available on the costs of IBD from the CEE countries^[22-25]. In a recently published paper within the framework of the Epidemiological Committee of European Crohn's and Colitis Organisation (ECCO-EpICom), costs for the first year of follow-up of newly diagnosed patients, including diagnostics and treatment, were estimated^[22]. In the CEE region (Croatia, the Czech Republic, Estonia, Hungary, Lithuania, Moldova, Romania, and Russia) annual per patient costs of CD comprised of the following items: diagnostics €1264, surgery €19586, standard treatment €324, and biologicals €9607, respectively, whereas those for UC were: diagnostics €740, surgery €14014, standard treatment €513, and biologicals €1729, respectively. Cost calculation was based on the Danish diagnosis-related group (DRG) financing system and costs of medications were encountered in Danish prices for all countries; thus, results should be interpreted with caution in the CEE^[22].

Direct healthcare costs attributable to IBD were investigated in Poland by Meder *et al.*^[23]. Between 2004 and 2007 medical costs of an acute exacerbation and a 12-mo follow-up period were calculated in 41 IBD patients, of whom 7 received surgical and 3 biological therapy. The average annual per patient costs of treatment amounted to €2968 in CD and €2540 in UC (EUR 1 = PLN 4.142). The bulk of direct costs were related to biological therapy and surgical treatment with mean annual per patient costs of €1565 and €692, respectively^[23].

In a multicentre study from Poland, indirect costs in 256 CD patients (aged 18-65 years, biological treatment rate not reported) were determined by a human capital approach (HCA)^[24]. Per patient mean annual costs attributable to absenteeism and presenteeism were €2348 and €3011, respectively

(EUR 1 = USD 1.344, year 2012)^[24].

Recently, Mandel *et al.*^[25] conducted a research on the indirect costs of IBD among 443 patients in Hungary. Applying the HCA method, average total annual per patient productivity loss was €1880, of which €1450 and €430 incurred due to disability-related productivity loss and sick leaves from work, respectively (EUR 1 = HUF 300, year 2013). Annual per patient costs of presenteeism in CD and UC patients were reported €2605 and €2410, respectively^[25].

ACCESS TO BIOLOGICAL THERAPY

So far, the following three biologicals have been registered for the treatment of IBD by EMA: adalimumab and infliximab for the treatment of CD; adalimumab, infliximab, and golimumab for the treatment of UC.

Numbers of gastroenterology centres entitled to administer biological therapy in the CEE countries are presented in Table 3. In the 9 selected countries, on average 784000 inhabitants are covered by a centre; nevertheless, in Romania and Latvia this exceeds the 2 million inhabitants per centre threshold, whereas in Estonia, Slovakia and the Czech Republic fewer than 500000 inhabitants are referred to each centre on average (Figure 1). We found a strong inverse correlation between the number of inhabitants covered by a centre and countries' total expenditure on health ($r = -0.83$, $P = 0.005$).

Due to the lack of IBD registries covering the entire patient population in the CEE countries, partial data on biological exposure are available *via* multiple sources such as health insurance databases, IMS sales statistics, ministries of health, national gastroenterology societies, and personal communication (Table 3). We provide an approximate estimation on biological treatment rates estimated from prevalence data of Table 2 and number of patients with biological therapy in Table 3: Hungary 19.1%, Slovakia 18.7%, the Czech Republic 11.3%, Estonia 3.9%, Lithuania 2.9%, Poland 2.8%, Romania 1.5%, Bulgaria 0.7% and Latvia 0.2%, respectively. Rates of UC patients treated with biologicals are as follows: Slovakia 6.4%, Hungary 3.5%, Romania 2.1%, Estonia 1.3%, Lithuania 1%, Bulgaria and Latvia 0%-0%, respectively. Taking into consideration the uncertainty in prevalence data, we also calculated the biological treatment rates based on the number of inhabitants for each country. (This approach disregards the differences in prevalence across the 9 countries.) Biological exposure rates are confirmed by the average number of patients treated with biologicals per 10⁵ inhabitants that shows similar distribution (Figure 2). However, these geographical access estimations need to be interpreted with caution since only patients aged ≥ 15 years were taken into consideration, and number of patients on biologicals aged < 15 is unknown.

Table 3 Number of Crohn's disease and ulcerative colitis patients treated with biologicals and centres where biologicals are administered in 9 selected Central and Eastern European countries, 2014

Country	Number of patients							Centres	
	CD ¹			UC ¹					Total
	Infliximab	Adalimumab	Total	Infliximab	Adalimumab	Golimumab	Total		
Bulgaria	NR	46	46	NR	0	NR	0	46	4
Czech Republic	750	240	990	412	NA	NA	412	1402	26
Estonia	29	13	42	21	5	1	27	69	4
Hungary	970	900	1870	460	170	0	630	2500	16
Latvia	1	2	3	0	0	0	0	3	1
Lithuania	30	43	73	15	31	0	46	119	4
Poland	506	382	888	NA	NA	NA	NA	888	50 ²
Romania	114	139	253	73	540	37	650	903	7
Slovakia	350	340	690	320	110	10	440	1130	13 ³
Total	2750	2105	4855	1301	856	48	2205	7060	125

¹Including paediatric and adult patients; ²Approximately; ³10 adult and 3 paediatric. National gastroenterology societies, ministries of health, IMS data, personal communication. NA: Not available; NR: Not reimbursed; CD: Crohn's disease; UC: Ulcerative colitis.

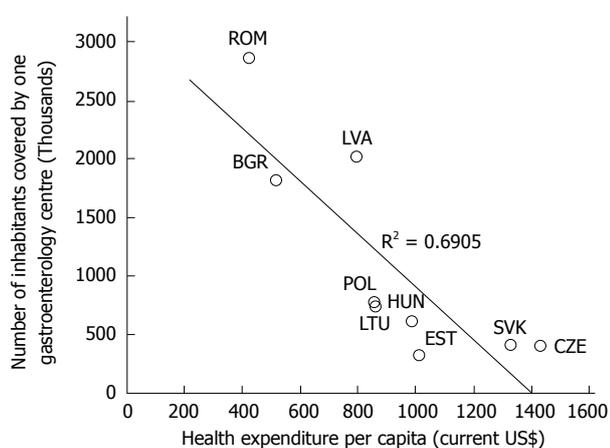


Figure 1 Number of inhabitants covered by one gastroenterology centre entitled to administer biological therapy in 9 selected Central and Eastern European countries, 2014. Population data: Eurostat Statistics Database (2013)^[24], total health expenditure per capita (2012): World Bank Databank^[26]. BGR: Bulgaria; CZE: Czech Republic; EST: Estonia; HUN: Hungary; LVA: Latvia; LTU: Lithuania; POL: Poland; ROM: Romania; SVK: Slovakia.

Price and reimbursement

To focus on prices of biologicals, some differences can be noted within the CEE region: adalimumab €957-€1262, infliximab €481-€617, and golimumab €1067-€1646 (per dose national list prices)^[5].

In most CEE countries, biologicals are covered at 100% by the health insurance system, although share of coverage between pharmaceutical companies and insurance funds occurs in certain countries. For instance, in Bulgaria 25% is paid by the pharmaceutical companies and 75% by the National Health Insurance Fund. Among the Baltic States, biological therapy is compensated by 100% in Lithuania and Estonia, but only 50% of medication cost is reimbursed in Latvia, where the other half is financed by patient co-payment. All three biologicals approved by EMA in IBD indication are reimbursed in CEE except for Bulgaria, where original infliximab and golimumab

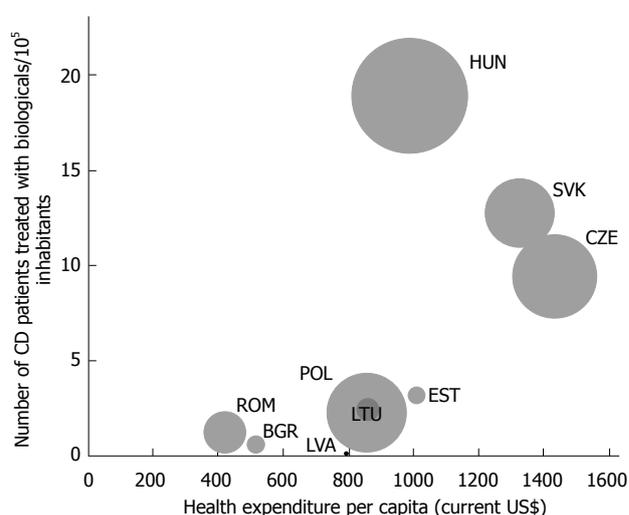


Figure 2 Average number of Crohn's disease patients treated with biologicals per 10⁵ inhabitants compared to countries per capita total expenditure on health. Ulcerative colitis would display a similar figure. Sizes of bubbles refer to the absolute number of patients treated with biologicals in each country. Data sources: patient numbers: IMS data (2014 or latest available), population data: Eurostat Statistics Database (2013)^[24], total health expenditure per capita (2012): World Bank Databank^[26]. BGR: Bulgaria; CZE: Czech Republic; EST: Estonia; HUN: Hungary; LVA: Latvia; LTU: Lithuania; POL: Poland; ROM: Romania; SVK: Slovakia.

do not have reimbursement coverage.

From 2014, biosimilar infliximab began to be marketed in the CEE countries resulting in a price reduction of approximately 20%-25%. In Hungary, since May 15, newly initiated biological therapy with infliximab must be undertaken with a biosimilar antibody. A mandatory switch is not recommended; however, relapsers should only be treated with a biosimilar if more than a year has passed since the termination of the previous biological therapy. A somewhat different regulation is applied in Poland, where new patients have to be treated with a biosimilar, and even patients receiving the original drug are forced to switch to biosimilar

infliximab as maintenance therapy. By contrast, in Romania, switch is not mandated, although in order to ensure a price level comparable to the biosimilars for patients, surplus costs generated by the prohibition of substitution are paid by pharmaceutical companies. In Lithuania, from August 1, biosimilar infliximab has to be the first-choice for all newly initiated biological therapies; however, the original antibodies are financed for patients on maintenance therapy with infliximab or adalimumab, and a switch is not allowed. The situation is unique in Bulgaria, where infliximab has not been reimbursed to date, and, hence, IBD patients skipping the original infliximab commence their first biological therapy with a biosimilar. On the other hand, in the Czech Republic either the originally released anti-TNF agents or the biosimilars can be used according to a physician's decision, and moreover, after the introduction of the biosimilars, prices of both the originally released and the biosimilar drug are required by law to be reduced by at least 15%.

Total per capita expenditure on health in the 9 CEE countries varied between \$420 (Romania) and \$1432 (Czech Republic) (year 2012)^[26]. We observed no significant correlation between the average number of patients treated with biologicals per 10⁵ inhabitants and total health expenditure (Figure 2). Despite Hungary, Poland, Lithuania, and Latvia having similar total expenditure on health, a higher proportion of patients per 10⁵ inhabitants was treated with biologicals in Hungary than in the other three countries. Furthermore, in Slovakia and the Czech Republic a lower proportion of patients per 10⁵ inhabitants received biologicals compared to their relatively high total health expenditure.

Eligibility criteria

Based on the current diagnostic and treatment recommendations of ECCO^[27,28], national gastroenterology societies have established their own guidelines. Several variations can be found across the CEE countries regarding the clinical criteria defined for eligibility to be treated with biologicals and in financing restrictions; we try to point out some notable differences between those countries, where criteria are clearly stated.

In most countries, moderate to severe luminal CD (Crohn's Disease Activity Index - CDAI > 300 in adults), or perianal or fistulising CD, or moderate to severe UC patients with immunosuppressant or corticosteroid refractory disease, or those with intolerance or contraindication to conventional therapies are eligible to be treated with biologicals. Efficacy of the induction therapy should be evaluated between weeks 12 and 16, and maintenance therapy is reimbursed for those who fulfil the response criteria (luminal CD: \geq 70 points decrease in CDAI; fistulising CD: \geq 50% reduction in the amount of drainage; UC: \geq 50% reduction in UCDAI; corticosteroid-resistant

UC: 3 points reduction in Mayo score; corticosteroid-dependent UC: corticosteroid-free remission).

In Bulgaria and Poland, CD patients' maintenance therapy is reimbursed only up to 12 mo; however, in Poland re-treatment is covered after 16 wk after the termination of the previous treatment. Criteria are more strict for UC, mainly severe patients are eligible to receive biological therapy, and additionally, treatment duration is also limited, for example, in Poland only three doses of infliximab without any further continuing treatment can be offered; and in Hungary, where UC patients' maintenance therapy is limited to 12 mo; nevertheless, during later flare-ups, retreatment is allowed.

Besides, different authorisation processes function that can affect the access in CEE. In general, gastroenterologists have to request for the biological drug from the health insurance company at the initiation of the therapy, and additionally they are obliged to report on therapeutic outcomes. During maintenance treatment, prolongation has to be claimed every 6 mo.

DISCUSSION

The objective of this paper is to review the access to biological therapy in IBD across 9 selected CEE countries. The proportion of patients treated with biologicals and average number of patients treated per 10⁵ inhabitants were estimated. Potential bias due to the unknown validity of country specific IBD epidemiology was filtered out using this population-based calculation.

In CEE, the estimated proportion of patients treated with biologicals vary from 0.2%-19.1% for CD and from 0%-6.4% for UC. In the United States, a recently published, retrospective analysis of a large database containing pharmacy and medical claims data of almost 1 million IBD patients indicates that 16.8% of CD and 3.5% of UC patients were treated with biologicals (infliximab, adalimumab, certolizumab pegol, natalizumab) between 2010 and 2012^[29]. This is similar to the treatment patterns of the best-performing countries from the CEE region.

In England, it is estimated that in CD and UC, 13% and 15% of the clinically eligible patients received biologicals in 2012^[30]. Thus, on average 26 CD patients were treated with biologicals (infliximab, adalimumab) per 10⁵ adults aged \geq 18 years which is higher than the rates observed in any of the CEE countries (Figure 2)^[30].

In all countries other than Romania, the lower biological treatment rates were observed in UC compared to CD despite the higher prevalence of UC. A possible explanation for the difference is that the first biological in UC indication was approved in 2007 (8 years after CD); therefore, due to the economic crisis and the subsequently implemented austerity

policies affecting health care spending as well, UC patients in these 9 CEE countries were disadvantaged compared to patients with either CD or with other systemic inflammatory conditions, where biological drugs had been used historically. Also, there are additional, non-economic determinants promoting treatment differences between CD and UC, *e.g.*, higher percentage of UC patients had their disease controlled with “conventional” therapies and the curative surgical option in medical failure^[31].

We tried to identify the most important factors that are underlying the differences in biological uptake among the CEE countries. Experts usually state that the following factors might influence the access to biologicals: differences in incidence and prevalence, price of biologicals, per capita total health expenditure, geographical access, clinical and financing guidelines, disease burden, cost-effectiveness results of biologicals, medical professionals’ lobbying power, local reimbursement policy, and health care financing mechanisms.

In CEE, access to biologicals is highly diverse, in certain countries such as Hungary, Slovakia, and the Czech Republic, higher number of patients per 10⁵ inhabitants are treated with biologicals, whereas in the Baltic States, Poland, Romania, and Bulgaria access to biologicals is rather limited. In addition to IBD, heterogeneous access to biologicals was reported from 6 CEE countries (Bulgaria, the Czech Republic, Hungary, Poland, Romania, and Slovakia) in other inflammatory conditions such as rheumatic diseases^[32]. Nevertheless, access rates in IBD vary more extensively across these six CEE countries. Compared to approximately an 8-fold difference noted in rheumatoid arthritis (Poland: 1.3% and Slovakia: 10%)^[32], we found up to 27-fold difference in CD (Bulgaria: 0.7%, Hungary: 19.1%). In addition, when considering all the 9 countries, that difference was as high as 96-fold.

Unfortunately, there are a lack of registries on IBD patients on biologicals, and up-to-date epidemiology are missing from some countries (Table 1). We presume, however, that variance in the incidence and prevalence of IBD does not explain such great differences in the access to biological therapy among these 9 countries. It should be addressed that establishing registries would allow not only follow up of patients, and provide valid and reliable data about access rates, but also might favourably enhance financing and reimbursement decision making concerning biologicals and additionally biosimilars.

The difference in the prices of infliximab, adalimumab, and golimumab in CEE^[33] does not explain the extent of heterogeneity for their access. Regarding the economic performance, the per capita gross domestic product (GDP) as a percentage of EU-27 countries’ ranges from 52.8% (Bulgaria) to 79.6% (the Czech Republic) resulting also a significant differences in total expenditure on health^[34]. As an example, the

Czech Republic spends 70% more on health compared to Romania and this might contribute to its 8-fold higher access rate. However, comparison of Hungary and Poland which have very similar total health expenditure refutes this assumption since in Poland the exposure to biologicals is approximately 10-fold lower compared to Hungary (Figure 2).

The number and geographic distribution of gastroenterology centres offering biological therapy can also affect the access in some countries. Nevertheless, Figures 1 and 2 indicate, that contrary to a comparable number of patients covered by a gastroenterology centre, Poland and Lithuania lag behind Hungary in terms of biological treatment rates.

Various reimbursement coverage of biologicals is possibly responsible for the diverse access rates in CEE. In all countries but Latvia (50% co-payment), biologicals are fully covered and do not require a co-payment. However, in Romania and Bulgaria, insurance funds and pharmaceuticals share the financing in a defined proportion. All countries apply eligibility criteria based on the ECCO guidelines as a standard for reimbursement, yet there can be marked variations among the countries in terms of severity of disease required and duration of reimbursed maintenance therapy. For example, in Bulgaria and Poland, the duration of maintenance treatment in CD and in Hungary for UC are limited to 12 mo. These obstacles likely contribute to the low access rates found in Poland and Bulgaria but not in Hungary, where despite the 12-mo stopping rule in UC, the highest number of UC patients per 10⁵ are treated with biologicals among the CEE countries.

Access to medications is largely determined by healthcare financing mechanisms. Most of the 9 countries share a similar policy and biologicals are covered under itemized financing; therefore, differences in biological uptake are not explainable by this factor. Additionally, in Hungary, a financing guideline on biological drugs draws up patient eligibility criteria. There is a unique situation in Lithuania, where a quota system was established based on the number of patients registered by treating centre, and only one in every four clinical centres could gain quotas to initiate new biological treatments. Thus, from August 1, 2014, a total of 23 new IBD patients will receive biological therapy within the next 12 mo in the whole country.

Most CEE countries have implemented a similar health technology assessment (HTA) based decision-making for reimbursement^[35]. It is unlikely that IBD is unfavourably distinguished in countries with established HTA, where reimbursement decisions require cost-effectiveness data^[35]. Neither variations of the estimated utility gain achievable until remission as a result of biological therapy (CD: 0.06-0.43, UC: 0.25-0.47) nor cost-effectiveness of biologicals can explain this access gap found between CD and UC in CEE^[36-39]. Utilities gained as a result of a therapy are used to generate quality-adjusted life years (QALYs).

QALY is a widely used outcome measure in cost-effectiveness analysis that takes into account both the length and the quality of life spent in a health state^[40]. A single abstract can be found concerning cost-effectiveness of biologicals from the CEE countries. In Poland, Goszczynska *et al.*^[41] conducted a study on cost-effectiveness of infliximab as an induction therapy in severe active UC. In a 12-mo timeframe an incremental cost-utility ratio for infliximab was estimated at €16896/QALY compared to colectomy that is below the official financing threshold (€24326/QALY) (EUR 1 = PLN 4.142)^[41]. Recently, Gulácsi *et al.*^[33] have estimated the cost-effectiveness of biologicals used in gastroenterology, rheumatology, and dermatology. According to the estimates, in the Czech Republic, Hungary, Poland, and Slovakia, cost-effectiveness results are below the threshold of 3 times per capita GDP/QALY applied in reimbursement decision making in many CEE countries. However, in Bulgaria and Romania under certain conditions this ratio exceeds the threshold^[33]. Hence, variations of cost-effectiveness ratios in six out of the 9 CEE countries do not justify the heterogeneity; for example, despite the calculated cost-effectiveness data in Poland, exposure to these drugs is rather low.

Finally, in the field of rheumatology many more patients are treated with biologicals than in IBD across the CEE countries^[32]. However, the prevalence of rheumatoid arthritis (RA) remains higher than that of IBD with a prevalence of 610/10⁵ inhabitants reported in the Czech Republic and a 0.5% prevalence in Hungary^[42,43]. In addition, comparison of utility gain achievable until remission as a result of biological therapy is estimated to be similar to CD (0.06-0.43), UC (0.25-0.47), and RA (0.15-0.40)^[36-39,44]. Interpreting these health gain findings requires caution. Possible methodological differences must be considered such as applied outcome measures, patients' baseline quality of life, time frames, and study design. Therefore, health gain differences cannot explain inequalities in access rates between IBD and RA.

CONCLUSION

Access to biologicals varies greatly (up to 96-fold) in the selected CEE countries that raises inequity concerns regarding access to treatment. To date, biological use in IBD in Poland, Bulgaria, Romania, and the Baltic States is much lower compared to Hungary, Slovakia and Czech Republic. The reason for this heterogeneity in the access to biologicals among the CEE countries has not been clarified. Differences in prevalence and incidence of IBD, prices of biologicals, total expenditure on health, geographical access, and cost-effectiveness results does not explain the above variation. Variations of reimbursement policy might explain the differences to a certain extent in Bulgaria, Latvia, Lithuania, and Poland. It may be also hypothesized that health disability linked to IBD

might be valued differently against other systemic inflammatory conditions in distinct countries. Further research, however, is needed to better understand the key factors contributing to the above differences and investigating future trends.

ACKNOWLEDGMENTS

Authors are grateful to Dr. Maciej Niewada (Health-Quest Consulting Company, Warsaw, Poland), Prof. Ludmilla Tankova (Gastroenterology Clinic, Queen Ioanna University Hospital, Sofia, Bulgaria), Prof. Juris Pokrotnieks (Stradins University, Riga, Latvia), and Ms. Neringa Venyte, (National Health Insurance Fund, Vilnius, Lithuania).

REFERENCES

- 1 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- 2 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]
- 3 **Nielsen OH**, Bjerrum JT, Seidelin JB, Nyberg C, Ainsworth M. Biological treatment of Crohn's disease. *Dig Dis* 2012; **30** Suppl 3: 121-133 [PMID: 23295703 DOI: 10.1159/000342738]
- 4 **Danese S**, Colombel JF, Peyrin-Biroulet L, Rutgeerts P, Reinisch W. Review article: the role of anti-TNF in the management of ulcerative colitis -- past, present and future. *Aliment Pharmacol Ther* 2013; **37**: 855-866 [PMID: 23489068 DOI: 10.1111/apt.12284]
- 5 **Brodzsky V**, Baji P, Balogh O, Péntek M. Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. *Eur J Health Econ* 2014; **15** Suppl 1: S65-S71 [PMID: 24832837 DOI: 10.1007/s10198-014-0595-3]
- 6 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]
- 7 **Lakatos L**, Lakatos PL. Is the incidence and prevalence of inflammatory bowel diseases increasing in Eastern Europe? *Postgrad Med J* 2006; **82**: 332-337 [PMID: 16679472 DOI: 10.1136/pgmj.2005.042416]
- 8 **Burisch J**, Pedersen N, Čuković-Čavka S, Brinar M, Kaimakliotis I, Duricova D, Shonová O, Vind I, Avnstrøm S, Thorsgaard N, Andersen V, Krabbe S, Dahlerup JF, Salupere R, Nielsen KR, Olsen J, Manninen P, Collin P, Tsianos EV, Katsanos KH, Ladefoged K, Lakatos L, Björnsson E, Ragnarsson G, Bailey Y, Odes S, Schwartz D, Martinato M, Lupinacci G, Milla M, De Padova A, D'Inca R, Beltrami M, Kupcinkas L, Kiudelis G, Turcan S, Tighineanu O, Mihiu I, Magro F, Barros LF, Goldis A, Lazar D, Belousova E, Nikulina I, Hernandez V, Martinez-Ares D, Almer S, Zhulina Y, Halfvarson J, Arebi N, Sebastian S, Lakatos PL, Langholz E, Munkholm P. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014; **63**: 588-597 [PMID: 23604131 DOI: 10.1136/gutjnl-2013-304636]
- 9 **Lakatos L**, Mester G, Erdelyi Z, Balogh M, Szipocs I, Kamaras G, Lakatos PL. Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977-2001. *World J Gastroenterol* 2004; **10**: 404-409 [PMID: 14760767]
- 10 **Lakatos L**, Kiss LS, David G, Pandur T, Erdelyi Z, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E, Lakatos PL.

- Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. *Inflamm Bowel Dis* 2011; **17**: 2558-2565 [PMID: 22072315 DOI: 10.1002/ibd.21607]
- 11 **Gheorghe C**, Pascu O, Gheorghe L, Iacob R, Dumitru E, Tantau M, Vadan R, Goldis A, Balan G, Iacob S, Dobru D, Saftoiu A. Epidemiology of inflammatory bowel disease in adults who refer to gastroenterology care in Romania: a multicentre study. *Eur J Gastroenterol Hepatol* 2004; **16**: 1153-1159 [PMID: 15489575]
 - 12 **Gregus M**. The incidence and prevalence of IBD in Slovakia. Oral presentation. Czech and Slovak IBD conference. *Prague* 2014
 - 13 **Hoivik ML**, Bernklev T, Moum B. Need for standardization in population-based quality of life studies: a review of the current literature. *Inflamm Bowel Dis* 2010; **16**: 525-536 [PMID: 19637337 DOI: 10.1002/ibd.21032]
 - 14 **Duricova D**, Pedersen N, Elkjaer M, Gamborg M, Munkholm P, Jess T. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies. *Inflamm Bowel Dis* 2010; **16**: 347-353 [PMID: 19572377 DOI: 10.1002/ibd.21007]
 - 15 **Bewtra M**, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. *Inflamm Bowel Dis* 2013; **19**: 599-613 [PMID: 23388544 DOI: 10.1097/MIB.0b013e31827f27ae]
 - 16 **Yu AP**, Cabanilla LA, Wu EQ, Mulani PM, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin* 2008; **24**: 319-328 [PMID: 18067689 DOI: 10.1185/030079908X260790]
 - 17 **Cohen RD**, Yu AP, Wu EQ, Xie J, Mulani PM, Chao J. Systematic review: the costs of ulcerative colitis in Western countries. *Aliment Pharmacol Ther* 2010; **31**: 693-707 [PMID: 20064142 DOI: 10.1111/j.1365-2036.2010.04234.x]
 - 18 **Bassi A**, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004; **53**: 1471-1478 [PMID: 15361497 DOI: 10.1136/gut.2004.041616]
 - 19 **Odes S**, Vardi H, Friger M, Wolters F, Russel MG, Riis L, Munkholm P, Politi P, Tsianos E, Clofent J, Vermeire S, Monteiro E, Mouzas I, Fornaciari G, Sijbrandij J, Limonard C, Van Zeijl G, O'morain C, Moum B, Vatn M, Stockbrugger R. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006; **131**: 719-728 [PMID: 16952541 DOI: 10.1053/j.gastro.2006.05.052]
 - 20 **Rocchi A**, Benchimol EI, Bernstein CN, Bitton A, Feagan B, Panaccione R, Glasgow KW, Fernandes A, Ghosh S. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol* 2012; **26**: 811-817 [PMID: 23166905]
 - 21 **van der Valk ME**, Mangen MJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, de Jong DJ, Pierik M, van der Woude CJ, Romberg-Camps PJ, Clemens CH, Jansen JM, Mahmood N, van de Meeberg PC, van der Meulen-de Jong AE, Ponsioen CY, Bolwerk CJ, Vermeijden JR, Siersema PD, van Oijen MG, Oldenburg B. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF α therapy: results from the COIN study. *Gut* 2014; **63**: 72-79 [PMID: 23135759 DOI: 10.1136/gutjnl-2012-303376]
 - 22 **Burisch J**. Crohn's disease and ulcerative colitis. Occurrence, course and prognosis during the first year of disease in a European population-based inception cohort. *Dan Med J* 2014; **61**: B4778 [PMID: 24393595]
 - 23 **Meder A**, Świątkowski M, Meder G, Koza J, Szamocka M. Treatment costs for the group of patients with non-specific inflammatory bowel disease during acute exacerbation and further annual observation. *Prz Gastroenterol* 2011; **6**: 36-44 [DOI: 10.5114/pg.2011.20106]
 - 24 **Wladysiuk M**, Fedyna M, Bebrysz M, Mateusz H, Rutkowski J, Owczarek W, Jahnz-Rozyk K, Gad B, Szmurlo D. Indirect costs of rheumatoid arthritis, Crohn's disease and psoriasis in Poland. Health Technology Assessment International Conference. Washington DC, 2014: 60
 - 25 **Mandel MD**, Bálint A, Lovász BD, Gulácsi L, Strbák B, Golovics PA, Farkas K, Kürti Z, Szilágyi BK, Mohás A, Molnár T, Lakatos PL. Work disability and productivity loss in patients with inflammatory bowel diseases in Hungary in the era of biologics. *Eur J Health Econ* 2014; **15** Suppl 1: S121-S128 [PMID: 24832845 DOI: 10.1007/s10198-014-0603-7]
 - 26 World Bank Databank. Available from: URL: <http://databank.worldbank.org/data/home.aspx>
 - 27 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
 - 28 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2009.12.002]
 - 29 **van Deen WK**, van Oijen MG, Myers KD, Centeno A, Howard W, Choi JM, Roth BE, McLaughlin EM, Hollander D, Wong-Swanon B, Sack J, Ong MK, Ha CY, Esralian E, Hommes DW. A nationwide 2010-2012 analysis of U.S. health care utilization in inflammatory bowel diseases. *Inflamm Bowel Dis* 2014; **20**: 1747-1753 [PMID: 25137415 DOI: 10.1097/mib.0000000000000139]
 - 30 National Institute for Health and Clinical Excellence. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Commissioning guide. 2012. Available from: URL: <http://www.nice.org.uk/media/F95/42/UpdateTA247AndPsoriasisCG.pdf>
 - 31 **Bernstein CN**, Ng SC, Lakatos PL, Moum B, Loftus EV. A review of mortality and surgery in ulcerative colitis: milestones of the seriousness of the disease. *Inflamm Bowel Dis* 2013; **19**: 2001-2010 [PMID: 23624887 DOI: 10.1097/MIB.0b013e318281f3bb]
 - 32 **Péntek M**, Poór G, Wiland P, Olejárová M, Brzosko M, Codreanu C, Brodszky N, Gulácsi L. Biological therapy in inflammatory rheumatic diseases: issues in Central and Eastern European countries. *Eur J Health Econ* 2014; **15** Suppl 1: S35-S43 [PMID: 24832834 DOI: 10.1007/s10198-014-0592-6]
 - 33 **Gulácsi L**, Rencz F, Péntek M, Brodszky V, Lopert R, Hevér NV, Baji P. Transferability of results of cost utility analyses for biologicals in inflammatory conditions for Central and Eastern European countries. *Eur J Health Econ* 2014; **15** Suppl 1: S27-S34 [PMID: 24832833 DOI: 10.1007/s10198-014-0591-7]
 - 34 Eurostat Statistics Database. Available from: URL: http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database
 - 35 **Gulácsi L**, Rotar AM, Niewada M, Löblová O, Rencz F, Petrova G, Boncz I, Klazinga NS. Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. *Eur J Health Econ* 2014; **15** Suppl 1: S13-S25 [PMID: 24832832 DOI: 10.1007/s10198-014-0590-8]
 - 36 **Bodger K**, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther* 2009; **30**: 265-274 [PMID: 19438428 DOI: 10.1111/j.1365-2036.2009.04033.x]
 - 37 **Chaudhary MA**, Fan T. Cost-Effectiveness of Infliximab for the Treatment of Acute Exacerbations of Ulcerative Colitis in the Netherlands. *Biol Ther* 2013; **3**: 45-60 [PMID: 24392304 DOI: 10.1007/s13554-012-0007-0]
 - 38 **Loftus EV**, Johnson SJ, Yu AP, Wu EQ, Chao J, Mulani PM. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 2009; **21**: 1302-1309 [PMID: 19465858 DOI: 10.1097/MEG.0b013e32832a8d71]
 - 39 **Punekar YS**, Hawkins N. Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *Eur J Health Econ* 2010; **11**: 67-76 [PMID: 19844750 DOI: 10.1007/s10198-009-0199-5]

- 40 **Weinstein MC**, Torrance G, McGuire A. QALYs: the basics. *Value Health* 2009; **12** Suppl 1: S5-S9 [PMID: 19250132 DOI: 10.1111/j.1524-4733.2009.00515.x]
- 41 **Goszczynska K**, Wrona W, Niewada M, Black CM, Fan T, Lobodzinski P. Cost-effectiveness of infliximab versus colectomy for the treatment of severe active ulcerative colitis in Poland. *Value Health* 2013; **16**: A213-214
- 42 **Hanova P**, Pavelka K, Dostal C, Holcatova I, Pikhart H. Epidemiology of rheumatoid arthritis, juvenile idiopathic arthritis and gout in two regions of the Czech Republic in a descriptive population-based survey in 2002-2003. *Clin Exp Rheumatol* 2006; **24**: 499-507 [PMID: 17181917]
- 43 **Lepp-Gazdag A**, Gulácsi L, Brandtmüller Á. A rheumatoid arthritis megbetegedés és ellátás jellemzői Magyarországon. *Egészségügyi Gazdasági Szemle* 2002; (6): 645-657
- 44 **Kobelt G**, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. *Ann Rheum Dis* 2004; **63**: 4-10 [PMID: 14672883]
- 45 **Bitter J**, Hulec J. [Ulcerative colitis in the North Bohemian Region]. *Cesk Gastroenterol Vyz* 1980; **34**: 137-144 [PMID: 7388984]
- 46 **Nedbal J**, Maratka Z. [Ulcerative colitis in Czechoslovakia]. *Vnitř Lek* 1967; **13**: 1054-1063 [PMID: 6081667]
- 47 **Salupere R**. Inflammatory bowel disease in Estonia: a prospective epidemiologic study 1993-1998. *World J Gastroenterol* 2001; **7**: 387-388 [PMID: 11819795]
- 48 **Kull K**, Salupere R, Uibo R, Ots M, Salupere V. Antineutrophil cytoplasmic antibodies in Estonian patients with inflammatory bowel disease. Prevalence and diagnostic role. *Hepatogastroenterology* 1998; **45**: 2132-2137 [PMID: 9951879]
- 49 **Nagy G**, Ujszaszy L, Juhasz L, Minik K. Epidemiology of inflammatory bowel diseases in Borsod-Abaúj-Zemplén county 1963-1992. *Lege artis Med* 1994; **4**: 424-430
- 50 **Zvirbliene A**, Kiudelis G, Kupcinskas L. [Retrospective analysis of case histories of patients with ulcerative colitis and Crohn's disease]. *Medicina (Kaunas)* 2003; **39**: 745-750 [PMID: 12960453]
- 51 **Kiudelis G**, Jonaitis L, Adamonis K, Žvirbliene A, Tamelis A, Kregždūtė R, Kučinskienė R, Šventoraitytė J, Kupcinskas L. Incidence of inflammatory bowel disease in Kaunas region, Lithuania. *Medicina (Kaunas)* 2012; **48**: 431-435 [PMID: 23128464]
- 52 **Chojceki Z**. Epidemiology of Ulcerative Colitis in Poland. *Pol Med Sci Hist Bull* 1964; **7**: 53-56 [PMID: 14152252]
- 53 **Wiercinska-Drapalo A**, Jaroszewicz J, Flisiak R, Prokopowicz D. Epidemiological characteristics of inflammatory bowel disease in North-Eastern Poland. *World J Gastroenterol* 2005; **11**: 2630-2633 [PMID: 15849823]
- 54 **Gheorghe L**, Gheorghe C, Aposteanu G. Clinical patterns and disease distribution in Crohn's disease in relationship to age at diagnosis. *Rom J Gastroenterol* 1997; (6): 147-152
- 55 **Toader EI**. Inflammatory bowel disease - a public health problem. *J Prev Med* 2008; **16**: 33-45
- 56 **Príkazská M**, Letkovicová M. [Crohn's disease in the adult population in Slovakia]. *Bratisl Lek Listy* 1996; **97**: 230-233 [PMID: 8689331]
- 57 **Príkazka M**, Letkovicová M, Matejčíková V. Crohns disease in Slovakia: prevalence, socioeconomic and psychological analysis. *Eur J Epidemiol* 1998; **14**: 49-53 [PMID: 9517873]

P- Reviewer: Caviglia R, Kozarek R, Liu F **S- Editor:** Ma YJ

L- Editor: A **E- Editor:** Ma S





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

