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Oncology monoclonal antibodies expenditure trends and reimbursement projections in the emerging Balkan market



ORIGINAL
RESEARCH

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ABSTRACT

Monoclonal antibodies applied in clinical oncology present a therapeutic promise for many patients with cancer. Nevertheless these expensive protocols are associated with extremely high acquisition and administration costs. The issue of societal affordability of such treatment options is particularly at stake among middle income European economies. Medicines Agency of Serbia issues regular annual reports on public expenditure on pharmaceuticals since 2004. According to these official data total public expenditure on drugs doubled from 2004-2012 (from € 339,279,304 to € 742,013,976). During the same nine years public expenditure on antineoplastic pharmaceuticals was rising at much faster pace, approximately five times from € 10,297,616 in 2004 to € 51,223,474 in 2012. Absolutely record growth belongs to the value of turnover of monoclonal antibodies indicated in diverse malignancies. These costs became almost twenty times higher in 2012 compared to 2004 (€ 19,687,454 towards € 1,033,313 in the past). National pharmaceutical expenditure trend projections in this country show strong recovery in 2012 after severe blow to the overall health care market imposed by the worldwide crisis. Universal health insurance coverage and sustainable health care financing provision will remain difficult issues for Balkan economies in years to come. Although monoclonal antibodies exhibit undisputed therapeutic efficiency in certain malignant disorders, cost-effectiveness estimates must be taken into consideration by policy makers deciding on reimbursement.

Keywords

Monoclonal antibodies, Pharmaceutical expenditure, Reimbursement

ECONOMIC BURDEN OF CANCER AND THE ROLE OF TARGETED ONCOLOGY PHARMACEUTICALS

One of the core determinants of global health is providing access and affordability of evidence-based care for major diseases. Health care needs and pharmaceutical spending growth in Europe continues to outpace overall economy growth due to population aging of nations and scientific innovation in medicine [1]. Among “prosperity diseases” cancer bears particular epidemiological and financial burden due its prevalence, clinical evolution, poor prognosis and long term [2]. Malignant disorders decrease significantly life expectancy and its quality, affect patient’s working ability and therefore threatens overall economic productivity of the society [3]. Cancer is ranked among top five illnesses according to their economic burden, among all industrial nations of northern hemisphere [4]. Besides pharmaceuticals and surgical procedures, some recent findings from this region indicate that radiation therapy and

imaging diagnostics are top cost drivers of cancer medical care [5,6].

During recent decades, substantial research and effort has been invested into development of monoclonal antibodies (mAbs) as novel, high profile pharmacological approach in cancer treatment [7]. Industrial production costs of mAbs, as well as in many other branches of pharmaceutical research and development (R&D) will likely decrease over time [8]. Domination of different mAbs within top blockbuster drug lists, gives us a hint on the vital meaning of these agents to the pharmaceutical industry profits worldwide [9,10].

Conventional cancer treatment protocols were compared to these cutting edge medical technologies. Some of them have undergone assessment in terms of evidence on their effectiveness and safety conducted by academia, governmental bodies and national drug agencies [11]. Each society has the interest to provide access to these medicines to most people who need it, among whom high clinical

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benefit is expected. There is still huge diversity in national policies towards mAbs reimbursement in the EU, regardless of EMEA's recommendations. Therefore access to targeted cancer immunotherapies to the citizens is still very much uneven across Europe [11]. In spite of proved clinical efficiency in many oncological indications due to difficult acquisition of such expensive agents, issues of reimbursement and affordability remain crucial [12].

This contribution intent was to provide insight into the local expenditure trends of monoclonal antibodies applied in clinical oncology. Such overview through the past decade in the largest country of the Western Balkans could be a picturesque example of what is happening in the broader Eastern European region. So far there is substantial knowledge gap on this issue in Serbia and surrounding countries. Unlike in many high income countries [13], there are few economic evaluations of mAbs based treatment protocols in published literature on Eastern European region [14,15].

PECULIARITY OF THE WESTERN BALKANS REGION

Eastern Europe and the Balkans region belong to the quite a different healthcare milieu comparing to the developed Western economies. Most countries have inherited from past socialist model of medical care funding and provision [16]. Lower medical labour wages mostly shape the landscape of service provision. It should be emphasized that drug acquisition costs follow global market pricing and remain only slightly lower than in the old pre-2004 EU members [17]. Electronic patient registries development still has to make bold steps ahead. Region is gradually succeeding to create more reliable statistics on morbidity and mortality - more precise diagnostics is being evidenced, more deceased are submitted to autopsy. Based on these trends, more reliable future estimates and planning shall be possible [18].

Registry for Serbian cancer population was established in 1970 on the basis of statistical research of interest for the Republic of Serbia. According to the last available edition of Health Statistical Yearbook of Republic of Serbia, incidence rate of all malignant tumours in the country was 26,663 cases while 15,042 patients have deceased in 2009 [19]. Epidemiological situation on cancer in Serbia is particularly difficult and serious compared to the EU average, because total incidence rates increased over 2.5 times while cancer-specific mortality rates increased approxima-

tely 1.5 times in only two decades from 1990 to 2010 [20]. There are probably several underlying reasons for such morbidity. Most frequently cited medical causes are proximity of Chernobyl [21], ecological consequences of 1990s military conflicts [22], post-war syndromes and unhealthy life style [23].

CURRENT SITUATION ON MABS AVAILABILITY AND ACCESS IN SERBIAN ONCOLOGY

Out of some 15 different generic compounds among monoclonal antibodies used to treat malignant disorders according to current WHO selection under ATC code L01XC [24] there are six drugs with currently positive marketing approval gained from the Medicines and Medicinal Device Agency of Serbia [25] in 2014. These are: pertuzumab, panitumumab, bevacizumab, cetuximab, trastuzumab and rituximab. Choice of these medicines varied slightly over time period observed (2004-2012) while some manufacturers were acquiring licences and others losing them. Although these drugs are marketed for a wider indication field, Republican Health Insurance Fund of Serbia has imposed reimbursement criteria with few strictly defined malignancies for each one of these drugs. It is single, central, state-owned, Eastern European-type fund in charge of most public health care facing difficult challenges in providing sustainable financing in recent years, mostly due to global economic crisis [17]. An example of Fund's restrictive policy is acknowledgment only of those drug acquisition costs which incurred during rituximab or cetuximab treatment of non-Hodgkin lymphoma; bevacizumab or cetuximab treatment of colorectal carcinoma and trastuzumab or rituximab treatment of breast cancer. These three malignancy groups were of particularly high relevance being among top four most expensive cancers to treat in the US in 2004, due to mAbs utilization [26]. Mabs based oncology protocols are administered only in few recognized tertiary university hospitals throughout the country. While keeping in mind middle income Western Balkans setting we should be aware that out of these indications, biological antineoplastics remain virtually unaffordable to the ordinary citizens if they have to be acquired via out-of-pocket expense [27].

Recently finished pioneering retrospective study on cancer economics reported first extensive data on costs of initial medical care of newly diagnosed cancer with mean value of € 6,949 (SD € 36,414) per patient within first six months since diagnosis [28]. These

data were acquired on a broad sample of over 1,200 patients with diverse ICD-10 diagnostic codes, stages and grades of disease. An excellent comparator to these data is provided by another ongoing local study focused on another prevalence-based sample of patients whose treatment protocols consisted of mAbs with adjuvant conventional cytostatic regimen. This study reported an average direct cost of medical care of € 13,658 in the approximately four month's long time horizon [29]. One could easily notice the pattern of almost two and a half fold higher total costs of hospital care among mAbs treated patients when compared to the ordinary patients regardless of clinical background data in Serbian setting.

Serbian national medicines agency (ALIMS) issues regular yearly reports on public medicines turnover and sales in the country. According to these reports total medicines related public expenditure grew twice from € 339,279,304 in 2004 to €742,013,976 in 2012 (Figure 1) [24]. In the same time public expenditure on antineoplastic pharmaceuticals grew faster, approximately five times from € 10,297,616 in 2004 to € 51,223,474 in 2012. One decade ago, according to the Agency's official release monoclonal antibodies entered the market in a shy manner representing only the minor portion of overall oncology therapeutics expenditure. Since 2004 its bud-

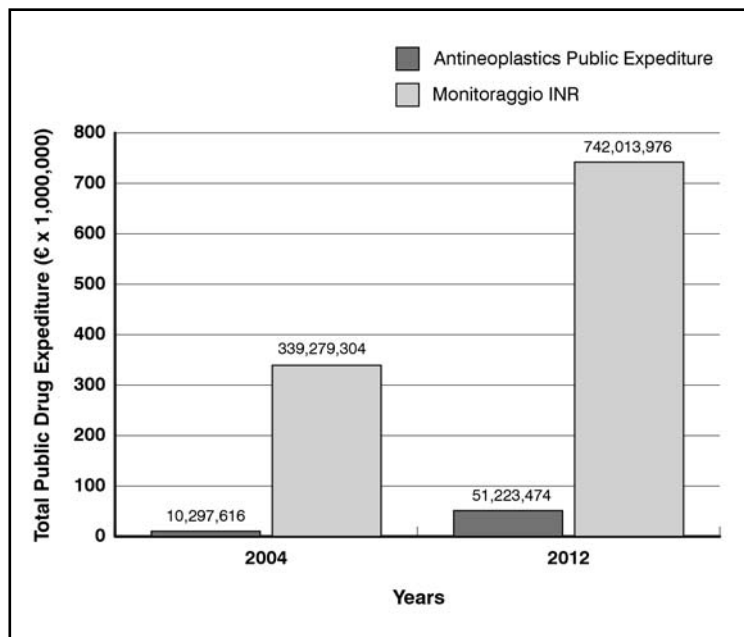


Figure 1. Increase in total public drug expenditure compared to the growth of overall antineoplastics expenditure (Serbia 2004-2012). Source of data: Medicines and Medicinal Device Agency of the Republic of Serbia – ALIMS [24]

get share among total antineoplastic drug acquisition costs was rising sharply and became by far the most dominant one already in 2006 (see Figure 2).

Recorded growth of market size in nine year term from € 1,033,313 (10.03 %) in 2004 up to the € 19,687,454 or 38.43 % in 2012. To-

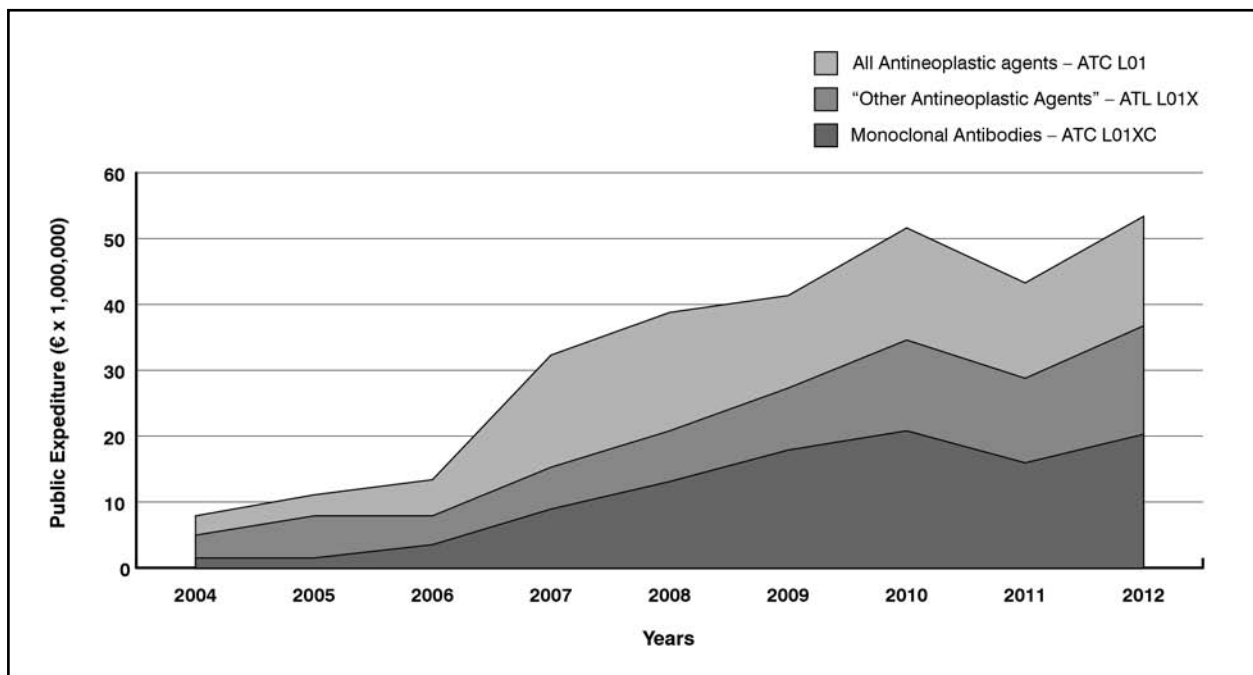


Figure 2. Public expenditure trend 2004-2012 on antineoplastic agents in Serbia (official exchange rates of National Bank of Serbia in respective years 2004-2012 were applied). Source of data: Medicines and Medicinal Device Agency of the Republic of Serbia – ALIMS [24]

* ATC code group L01 expressed as volume of sales in Euro values

° ATC drug code groups' clarification. ATC code group L01 encompasses: alkylating agents, antimetabolites, plant alkaloids and other natural products, cytotoxic antibiotics and related substances, other antineoplastic agents (L01X). The last subgroup further consists of platinum compounds, methylhydrazines, monoclonal antibodies, sensitizers used in photodynamic/radiation therapy, protein kinase inhibitors, other antineoplastic agents and combinations of antineoplastic agents

tal oncology related drug acquisition costs in the public health care sector amounted from € 10,297,616 in 2004 to € 51,223,474 in 2012 respectively [24]. This means that the increase in total expenditure on antineoplastic pharmaceuticals was five times while increase in mAbs consumption was almost twenty times in terms of absolute value in only nine years time span. Mabs prescribing and consumption financially clearly far outpace total oncological drug expenditure growth. These findings nationwide are in line with reported unit consumption of mAbs in a local university clinic in Serbia [30].

Observing the data on public consumption and sales given on the graph 2 we can notice strong rise in market demand and sales from 2004 up to the 2010 and then sudden drop in 2011 with strong recovery trend upwards in 2012, slightly overstepping 2010 limit. This happened due to consequences of worldwide economic crisis in the region as well as due to transitional difficulties related to national health systems reforms from Soviet to Western market oriented models [5]. Although the official data on drug sales for 2013 are still lacking, according to our data for 2012 and most pharmaceutical market forecasts, steady recovery is to be expected in following years [31]. It should also be noted that national drug agency of Serbia has insight only into public, state-owned hospitals and pharmacists reported utilization of medicines. This is an important limitation in many therapeutic areas for interpreting data, because of lacking private sector sales which add substantial value to the market size. In case of biological drugs administered in the specialist oncology clinics this is less relevant because these protocols are so far administered only in few key referral public university hospitals throughout the country [32].

CONCLUSIVE REMARKS

While total medicines related public expenditure in Serbia 2004-2012 became approximately only twice higher, antineoplastic pharmaceuticals expenditure grew five times. In the same period mAbs prescribing and consumption value have overrun this trend with almost twenty times increase.

Regardless of evidence on clinical effectiveness, mAbs oncology protocols may have

unbearable budget impact in some low and middle income national health systems [33]. Due to particularly decisive influence to the overall antineoplastics expenditure planning, mAbs prescribing must be firmly grounded in clinical guidelines as well as in cost-effectiveness estimates [34]. Previous studies have shown that it is possible to reshape clinician's prescribing behavior with evidence based guidelines [35]. Higher awareness of clinicians on cost limitations and necessity of prioritization in health care funding would provide wiser allocation of scarce resources and better access to the quality medical care to the citizens.

Another key strategy intended to control sky rocketing costs of mAbs in clinical oncology [36] was complex generic substitution policy such as the one promoted in Japan [37]. Nevertheless, because of demanding technology of monoclonal antibodies production [38] appearance of generic mAbs is yet to be awaited in the world market [39].

Third commonly applied policy pattern was noticed response of Serbian authorities to the difficulties of health care financing – introduction of limitation criteria for mAbs reimbursement. In this scenario these medicines are administered only to the narrow selection of patients who are most likely to benefit from the treatment and/or least likely to experience serious adverse events [40].

An effort should be invested to exert pressure on higher ranked officials in the Ministry of Health and National Health Insurance Fund to implement health economics tools into clinical practice. Evidence based resource allocation should be more systematically applied to the clinical decision making particularly in technologically most demanding and expensive branches of medicine [41]. For this purpose substantial efforts are needed to persuade decision makers emphasizing them the opportunities for long-term savings while preserving clinical benefit coming from these drugs.

We should never forget the key role of these expensive targeted immunotherapies to the improved survival in many patients with diverse clinical entities of disease, stage and grade upon diagnosis [4]. Further R&D investment on highly specific biological agents has yet to bring hope to many patients with poor prognosis at the present level of knowledge [42]

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