Targeted Therapy and Its Availability in Serbia

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SUMMARY
Targeted therapy has made a significant breakthrough for the treatment of different kinds of severe diseases, mostly oncological and autoimmune ones. Biological or biotech products, as well as small synthetic molecules, like family of tyrosine kinase inhibitors, have already expressed their efficacy in several important indications. Their availability on the market and reimbursement possibility is of great importance, especially for the patients needed to be on lifelong therapies. Targeted therapy enhanced progression free and overall survival in many conditions, but also a number of these therapies produced important and severe side effects. Considering the fact that targeted therapy is on the global market relatively shortly, there is necessity for prolonged therapy monitoring: for further effectiveness assessment, for safety profile and long term health consequences establishment. Reimbursed targeted therapy proved its benefits that overweight risks, but still remains extremely high costs problem for its application. For an upper middle income country like Serbia, with significantly lower health care expenditures per capita than in other well developed countries, the availability of this expensive therapy is not yet gratifying.

Keywords: targeted therapy; biological; costs; reimbursement; Serbia

INTRODUCTION
Targeted therapy made a significant breakthrough for the treatment of different kind of severe diseases, like malignancies, neurological diseases, hepatitis, anemia and other kinds of autoimmune ones. Comparing to the conventional therapy, it offers advantages in cell-specific mechanism of action. Its acute toxicity profile differs from cytotoxic therapy and shows stunning improvement in patient survival and disease remission. However, taking into consideration that many modified cellular signaling pathways are of substantive importance for growth or homeostasis of normal cells, there is still not enough clinical experience for prolonged period of utilization and of long term toxicity profile of these drugs [1]. Drugs for targeted therapy are mostly biological or biotech products, but there are also small synthetic molecules, like family of tyrosine kinase inhibitors, that expressed their efficacy in several indications. Their availability on the market and reimbursement are of great importance, especially for patients needed to be on lifelong therapies.
EXPENDITURE FOR HEALTH CARE AND PHARMACEUTICALS

Spending for health care and pharmaceuticals are useful indicators for obtaining picture of overall drugs funds and therefore their availability. In European Union (EU) countries, expenditure for health care was rising until 2010 and reached more than 9% of Gross Domestic Product (GDP), in average. Slowdown in growth of healthcare spending in 2010 occurred, but still achieving 9% of GDP [2]. Health expenditure per capita in Serbia, for year 2011, was 622 USD (or 479 EUR) and 10% of GDP [3], which was, as expected, much less than in, e.g. Norway and Switzerland, two European countries with largest spending per person (more than 4,000 EUR) [2].

Spending on pharmaceuticals is the third biggest component (with 19%) of all healthcare expenditure, on average, in EU member states. In Serbia, 279 EUR per capita was spent on prescription drugs and OTC in 2010, which was a more than 30% of total health expenditure. For hospital setting, hospital medicines cost 15% of all expenses for prescription and self-medication drugs [2].

In Germany, where annual health care costs 3,300 EUR and pharmaceutical spending of almost 500 EUR per capita [2], biotech drugs accounted for 13% of all pharmaceutical spending represented with 4% of prescriptions [4]. Annual therapy cost per patient of most biotech drugs could mount up to 70,000 EUR and for rare genetic diseases more than 200,000 EUR [5]. Therefore, urgent need for costs monitoring and their cutting, on the one hand, and necessity of targeted therapy availability, on the other, has to be balanced.

A worldwide trend is observed that the rate of approved new drug entities slowed down, and a number of biosimilars and “me too” biotech drugs grow up. However, biopharmaceutical sector represents a significant part of pharmaceutical market. In 2007, value of all biologics sales was 16% of all pharmaceutical market [6].

As expected, a half of the total number of biotech companies is geographically located in US (216), in Europe (134) and the rest other in the world. Ten top selling biologic drugs of 2011, on global market, were: adalimumab, etanercept, rituximab, infliximab, bevacizumab, trastuzumab, pegfilgrastim, ranibizumab, interferon beta 1-a and interferon beta 1-b [7]. It is obvious that 60% of them are monoclonal antibodies (mAbs). Monoclonal antibodies accounted for almost half of all biopharmaceutics’ sales in 2010, which mounted up to USA $ 108 billion [8].

REIMBURSED BIOLOGICAL DRUGS IN SERBIA

Biological medicinal products are recognized by Serbian law on medical products and medical devices [9], including immunological drugs (vaccines, serums, allergenic extracts), blood and blood products, gene therapy products and bioengineered drugs obtained from tissue and cellular cultures. Many of them are available to patients under national health insurance coverage and are included in the national List of medicines [10]. Biological medicinal products, as well as other targeted therapy drugs, as a part of different ATC groups of drugs, are listed among the ones used mostly in hospital settings and with specific routs of administration. The most expensive drugs, with specific rules of prescribing, such as monoclonal antibodies, erythropoietins, proteasome inhibitors, interferons, etc. are ranked in special part of national drug list (so called “List C”). They could be obtained for certain indications and under specific conditions, for each of these drugs.

Erythropoietin

Group of antianemic preparations, for symptomatic anemia treatment in patients with chronic kidney failure, is represented by erythropoietin alfa, beta and zeta, darbepoetin alfa and methoxy polyethylene glycol-epoetin beta in the Serbian List of medicines [10].

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursor of the stem cell compartment. The protein fraction of the molecule consists of 165 amino acids. Epoetin alfa obtained by gene technology is glycosylated and identical in its amino acid and carbohydrate composition to endogenous human erythropoietin [11]. Erythropoietin is the principal regulator of the process of erythropoiesis, which maintains an optimal circulating red cell mass for oxygen delivery to the tissues [12]. It binds to and activates specific receptors on red cell progenitors in the bone marrow. Signal transduction via the erythropoietin receptor prevents apoptosis of erythroid
cells, permitting their further proliferation and differentiation into mature erythrocytes [13]. The subsequent increase in red cell mass occurs and improves tissue oxygenation [14].

Biosimilar erythropoietins are among first biosimilar drugs available on the global market, since 2007, when patent protection expired for the original epoietin alpha (Eprex®) [15]. For demonstration of similar efficacy of biosimilar epoetin and the originator, if change from baseline in hemoglobin is used, as the primary endpoint, European Medicines Agency (EMA) considers acceptance range of ±0.5 g/dL in blood hemoglobin concentrations, within 95% confidence interval. In terms of clinical safety, the use of a validated, highly sensitive antibody assay is mandatory, able to detect both early (low affinity antibodies) and late (high affinity antibodies) immune responses [16].

In research studies, it is shown that the quality of biosimilar epoetins is high, and the various epoetin products have major differences in potency and possible impact on immunogenicity toward their isoform composition [17]. Main impediments in erythropoietins usage remain their immunogenicity (formation of neutralizing antibodies), costs and parenteral administration [14].

Rituximab

Rituximab is a chimeric mAb, reimbursed by Serbian National Health Insurance Fund (NHIF) for following indications: non-Hodgkin’s lymphoma (NHL) and rheumatoid arthritis (RA) [10]. It is the first mAb approved in US for cancer treatment, and later for RA, in combination with methotrexate. Theoretically, rituximab could be used for treatment of every disease in which B lymphocytes play an essential role. B cells are antibody producing and antigen presenting cells, thus in theory most auto-immune diseases could be treated and benefit from rituximab [18].

The Fab domain of rituximab binds to the transmembrane antigen CD20 on B lymphocytes and the Fc domain can recruit immune effectors functions to mediate B cell lyses. CD20 is expressed on more than 95% of all B cell non-Hodgkin’s lymphomas [19].

B cells are probably playing a role in the pathogenesis of RA and associated chronic synovitis. The B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation and/or proinflammatory cytokine production [20]. In addition of the approved indications for rituximab, there are many clinical trials conducting, in order to confirm, where applicable, off-label use of difficult-to-treat autoimmune diseases [18]. However, there have to exist activities for the pharmacovigilance and interventions detailed in the agreed Risk Management Plan presented in the official documents and obligations by law. Hypersensitivity to the active substance and active, severe infections remain main contraindications for therapy with this mAb [19]. There are still no registered biosimilars of rituximab in the global market.

Trastuzumab

Among breast cancers diagnosed at any stage, 20-30% are found to have amplification of the human epidermal growth factor receptor (HER2) and consequently over expression of a trans membrane protein with tyrosine kinase activity [21]. Trastuzumab (Herceptin®) is a recombinant humanized IgG1 mAb, indicated for the treatment of patients with HER2 positive metastatic breast cancer as monotherapy or in combination with other chemotherapeutics; it is reimbursed by NHIF for this indication. Additionally, it is indicated for the treatment of patients with metastatic gastric cancer whose tumors have HER2 over expression. It was first approved by the FDA, in 1998. Trastuzumab binds with high affinity and specificity to HER2 extracellular domain, inhibits ligand-independent HER2 signaling and prevents an activation mechanism of HER2. As a result, inhibition of the proliferation of human tumor cells that over express HER2 occurs [22]. The main problem of trastuzumab therapy remains heart failure that has been observed in patients receiving Herceptin® therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline–containing chemotherapy. Therefore, all potential patients for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide exposure, should undergo baseline cardiac assessment and a careful risk-benefit assessment should be made before deciding to treat with trastuzumab [23]. At last, significantly high annual costs for trastuzumab treatment...
which could reach up to 70,000 USD, should be taken into consideration [24].

Cetuximab

First approval of cetuximab for the treatment of patients with advanced colorectal cancer was by FDA in 2004. After one year, at the beginning of 2006, indication was expanded, and it was used for the head and neck cancer patients’ treatment [25]. There are still no therapeutic equivalents to this biotech drug. Erbitux® (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Erbitux is indicated for the treatment of K-Ras mutation-negative (wild-type), epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) [26]. It has been shown to increase overall survival in mCRC by about 4-5 month in chemotherapy refractory disease [27]. Adverse reactions from this mAb include common injection reactions, rash, diarrhea, venous thromboembolic events and electrolyte abnormalities. There is no benefit of addition of another mAb to standard chemotherapy combination [1].

Bevacizumab

Bevacizumab (Avastin) is recombinant humanized monoclonal IgG1 antibody, indicated for use in combination with other chemotherapeutic agents in metastatic colorectal carcinoma, metastatic breast cancer, non-small cell lung cancer, advanced and/or metastatic renal cell cancer and ovarian cancer [28]. It is mAb against the ligand of vascular endothelial growth factor receptor (VEGFR). It is believed that VEGFR pathway plays an important role in a many malignant diseases. First approval of bevacizumab was in 2004, by FDA, and indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum; since 2006 and afterwards, new indications for treatment of non small cell lung cancer, glioblastoma and renal cell carcinoma, were added [29]. First marketing authorization in Europe was in 2006, by EMA. In Serbia, therapy with this mAb is reimbursed only for metastatic colorectal cancer use. There are still no therapeutic equivalents to this drug on the market. It has already been established that bevacizumab use with irinotecan plus 5-fluorouracil and leucovorin combination increases overall survival in metastatic colon cancer approximately by 4 months [30]. Addition of bevacizumab to adjuvant chemotherapy has not shown any benefit, as well as addition of other mAbs [1]. However, increase in adverse reactions associated with bevacizumab was seen, which included gastrointestinal perforation, arterial thromboembolic events, bleeding events, wound healing complications, hypertension [31].

Imatinib

Imatinib is one of the families of tyrosine kinase inhibitor molecules, which potently inhibits the Bcr-Abl tyrosine kinase. It selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines, as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) patients. First imatinib licensed product (Glivec®) in EU was authorized by EMA in 2001, and it is indicated for treatment of CML, ALL, unrespectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) [32]. Since the introduction of imatinib for treatment of CML, studies have shown that almost 80% of all treated patients had progression free and overall survival. It is even estimated that majority of patients with CML have normal life expectancy [1]. From the beginning of 2013 new imatinib containing drugs have got marketing authorization in EU (Imatinib Teva®, Imatinib Actavis®). There are 2 imatinib products that are reimbursed by NHIF for patients with CML and GIST in Serbia. This drug is orally administered and shows large efficacy in CML, without substantial toxic effects, as shown in has been shown in different clinical studies [33]. Observed common adverse effects are severe fluid retention, infection, unexpected bleeding and some other uncommon or rare side effects [32]. The benefits of treatment with imatinib, accompanied by adverse effects, have to be managed to ease a patient’s adherence to this significant therapy.

Gefitinib, erlotinib, sunitinib, lapatinib, nilotinib

A large number of tyrosine kinase inhibitors (TKIs) have been developed and have shown
success in treating different malignant diseases. Some of them are reimbursed by Serbian NHIF for different indications: non-small cell lung cancer (gefitinib), lung adenocarcinoma (erlotinib), metastatic renal cell carcinoma (sunitinib), breast cancer (lapatinib) and CML (nilotinib) [10]. All TKIs have the same mechanism of action, mostly competitive ATP inhibition at the binding site of tyrosine kinase, but they differ from each other in spectrum of targeted kinases [34].

Erlotinib and gefitinib are targeting mutated active epidermal growth factor receptor (EGFR) and showed approximately 6 month improvement in progression free survival in patients with non-small cell lung cancer compared with conventional chemotherapy [35]. Advantage of TKIs therapy is also their oral route of administration. Main adverse effects are due to exerting their cytotoxic effects. Problem in therapy also begins with cell resistance through mutations in the kinase gene that leads to decreasing of drug binding. TKIs mostly evoke different adverse effects on skin and hair (erlotinib and gefitinib), hemorrhage and edema (sunitinib), hematological side effects and cardiac toxicity [34].

However, benefit in overall survival achieved in the therapy with these drugs over-weight mostly side effects. Still, remains need for carefully balanced administration and getting new data of long-term side effects, since the relatively short period of time they have been approved for the treatment [1].

**Bortezomib**

An essential role in regulating homeostatic and cellular events involved in cancer genesis plays ubiquity – proteasome pathway. Bortezomib (Velcade’) is the first proteasome inhibitor approved by FDA in 2003, than in 2004 by EMA, as antineoplastic drug for treatment of multiple myeloma patients [36, 37, 38]. It has demonstrated apoptotic inducing activity in a multiple tumor cell lines. Less encouraging results then in hematological malignances have been obtained using bortezomib in treatment of solid tumors, but, at the moment, it is tested in combination with other conventional chemo-therapeutics and radiotherapy in such indications [39]. In patients with regressed multiple myelomas, bortezomib as monotherapy showed significant increase in overall survival period [40]. The most common adverse effects of bortezomib treatment are peripheral neuropathy, hypotension, cardiac and pulmonary toxicity, thrombocytopenia and hepatic toxicity [36].

**Interferons**

Interferons (IFNs) are integral part of native immune response to pathogen-associated molecular patterns. There are various IFNs subtypes and their immunomodulatory, antiviral and anticarcinogenic properties are researched extensively [41]. For the therapeutic use, several formulations of interferon are on the market in Serbia and reimbursed: interferon beta 1a (Avonex, Rebif), interferon beta 1b (Betaferon); conjugated (pegylated) forms of interferons: peginterferon alfa 2b (Pegintron) and peginterferon alfa 2a (Pegasys) [10]. Interferons beta 1a and 1b are used for treatment of patients with multiple sclerosis, a chronic neurological condition that is characterized by neuronal inflammation and demyelization. In spite of possible forming of neutralizing antibodies against IFN beta, long term efficacy has been proven [41, 42]. Pegylated interferons alfa are the standard of care in combination with some other antiviral drugs for chronic hepatitis B and C infection. IFNs are not reimbursed by NHIF for use in other indications, as in advanced renal cell carcinoma, even though survival benefit exists when combined with anti-VEGF mAb – bevacizumab [43].

IFNs could provoke common side effects, like flu-like symptoms, lethargy, autoimmune disease, myelosupression, neutropenia, depression, pneumonitis and pulmonary arterial hypertension [44].

**Glatiramer acetat**

Multiple sclerosis (MS) is a chronic, inflammatory disease of CNS, characterized by multifocal demyelization, neuronal and axonal damage followed by sclerotic plaques formation in any part of CNS. Glatiramer acetate is a synthetic analogue of myelin basic protein (MBP), an antigen involved in MS pathogenesis. It blocks MBP from binding to lymphocytes - antigen presenting cells on the periphery and impedes their stimulation [45]. This drug is used in therapy since its first approval by FDA, in 1996. It is indicated for use in ambulatory patients with relapsed remittent multiple sclerosis for reduc-
tion of relapses, but not in primary or secondary progressive MS. The very common adverse reactions to this drug are infection, influenza, anxiety, headache, vasodilatation, dyspnea, chest pain and injection site reactions [46].

**Tumor necrosis factor alpha inhibitors (etanercept, infliximab, adalimumab, golimumab)**

Treatment of rheumatoid arthritis, as a chronic autoimmune inflammatory disease, demands application of conventional disease-modifying antirheumatic drugs (cDMARDs) in a first line treatment. If suboptimal response or intolerance occurs, then biological DMARDs are value alternative [47]. Tumor necrosis factor alpha (TNFα) inhibitors are substantial part of this group of drugs.

Etanercept is a human TNFα receptor fusion protein, produced by recombinant DNA technology. It binds to and neutralizes the biological activity of TNF, therefore preventing TNF mediated signal transduction. It is indicated for treatment of moderate to severe RA in combination with methotrexate or as monotherapy, as well as for juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis [48]. It is authorized for the first time in Europe in 2006. It showed significantly better results in reduction of disease activity and improvement of functional disability [49].

Infliximab is a chimeric monoclonal antibody that binds with high affinity to TNFα. It is reimbursed for treatment of Crohn's disease, ulcerative colitis, as well as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. A decision analytic model constructed in order to obtain risks and benefits of infliximab in Crohn's disease showed that comparing with standard therapy, infliximab resulted in more quality-adjusted life years (QALYs) per patient [50]. Very common undesirable effects of infliximab were viral and bacterial infections, blood and lymphatic system disorders, abdominal pain and nausea, increased transaminases and infusion related reactions [51]. Rare but serious complications are lymphoma, sepsis and death, but in properly selected patients, benefits overweight risks associated with infliximab administration [50].

Adalimumab is recombinant human mAb which acts similarly like infliximab, by binding with high affinity to TNFα [52]. This biological DMARD is reimbursed for the same indications as infliximab, and showed similar efficacy and tolerability, with similar annual costs of therapy [53].

Golimumab is a novel anti-TNFα blocker, full human mAb, acting on both forms of TNFα. It is approved for rheumatic arthritis, psoriatic arthritis and ankylosing spondylitis. Golimumab showed significant improvement in patients with ankylosing spondylitis compared to placebo, as well as in patients with rheumatoid arthritis in combination with methotrexate vs. methotrexate alone. The main adverse effects with this drug are infections, abnormal liver function, hypertension and some cases of malignancies [54].

**Tocilizumab**

Tocilizumab is indicated for treatment of RA in patients with no adequate response with conventional or biological DMARDs. Its mechanism of action differs from other bDMARDs, since it is recombinant monoclonal IgG1 anti-human IL-6 receptor (IL-6R) antibody [55]. Tocilizumab showed superiority in many clinical studies comparing to methotrexate therapy, and it showed response in patients who failed to respond to anti-TNF blockers therapy [56]. Its safety is favorable for both short-term and long-term treatment. Adverse effects were less severe compared to other biologic therapies, predominantly infections occurred [55].

**FUTURE DIRECTION AND CONCLUSIONS**

There is no doubt that targeted therapy made a significant step forward in treatment of different, life-threatening and long-lasting diseases. It enhanced progression free and overall survival in many conditions, but also a number of these therapies produced important and severe side effects. Some of them could be tolerated for a short time period, but for lifelong therapies, it is difficult to obtain acceptable patients' quality of life or even avoid life threatening conditions. Considering the fact that targeted therapy is on the global market relatively briefly, there is necessity for prolonged therapy monitoring: for further effectiveness assessment, for safety profile as well as for long term health consequences establishment. Reimbursed targeted
therapy proved its benefits that overweight risks, but still remains extremely high costs problem for its application. For an upper middle income country like Serbia, with significantly lower health care expenditures per capita than in well developed countries, the availability of this expensive therapy is not yet gratifying.

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Conflict of Interest Statement

The authors certify that there are no potential conflicts of interest.

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Lekovi za ciljanu terapiju i njihova dostupnost u Srbiji

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KRATAK SADRŽAJ
Ciljana (molekulska) terapija je značajno napredovala, naročito u lečenju najtežih, pretežno on-košolčkih i autoimunskih bolesti. Mnogi biološki ili biotehnološki proizvodi, kao i mali molekuli, kao što su inhibitori tirozin-kinaza, dokazali su svojoj efektivnosti u nekim važnim indikacijama. Zbog toga je vrlo značajna njihova dostupnost na tržištu i mogućnost refundiranja, naročito za bolesnike koji bi trebalo da doživotno primaju ovu terapiju. Ciljana terapija povećava dužinu i ukupno preživljavanje u mnogim stanjima, ali mnogi ovi lekovi izazivaju i teške neželjene reakcije. Uzimajući u obzir činjenicu da je ciljana terapija na svetskom tržištu relativno kratak vremenski interval, potreban je nadzor nad primenom ovih lekova tokom dužeg perioda, prvenstveno da bi se utvorili njihova dalja delotvornost, sigurnosni profil i dugoročne posledice po zdravlje bolesnika. Lekovi za ciljanu terapiju koji se refundiraju dokazali su da njihovom upotребom korist prevazilaziti rizike. Međutim, i dalje ostaje problem izuzetno visokih troškova njihovog korišćenja. U Srbiji, koja se ubraja u srednje razvijene zemlje na osnovu brutno doma-čeg prihoda, troškovi za zdravstvo po glavi stanovnika su znatno niži nego u dobro razvijenim zemljama, i zbog toga dostupnost ciljane terapije još nije na zadovoljavajućem nivou.

KLJUČNE REČI: ciljana terapija; biološki lekovi; troškovi; refundiranje; Srbija