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ANALYSIS OF BIOLOGICAL TREATMENTS IN PATIENTS WITH MULTIPLE SCLEROSIS IN ESTONIA

Master's thesis

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SCLEROSIS MULTIPLEX'I BIOLOOGILISE RAVI ANALÜÜS EESTIS

Magistritöö

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Tallinn 2018

Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

The aim of this thesis is to develop a model to analyse usage, cost and need of biological treatments in Estonia based on biological treatment used on patients with multiple sclerosis as a model. The aim is achieved by comparing the quality and availability of data in different databases.

A statistical analysis was performed by using different databases (the State Agency of Medicines, the Estonian Health Insurance Fund and hospital databases). In addition, interviews were conducted with area experts.

The results of synthesis and comparison of data demonstrate that even though databases provide various data, obtaining a full and comprehensive picture of the situation is complicated due to different limitations of databases. However, the trends of usage and cost can be inferred rather clearly.

This thesis is written in English and is 78 pages long, including 6 chapters, 24 figures and 7 tables.

Annotatsioon

Sclerosis multiplex'i bioloogiline ravi analüüs Eestis

Bioloogiline ravi on elusorganismi poolt toodetud või sellest saadud ainet toimeainena sisaldavad ravimid, mida toodetakse biotehnoloogilistel meetoditel. Bioloogiline ravi on äärmiselt efektiivne, kuid ka kulumahukas.

Töö eesmärk: Analüüsida bioloogilise ravi kasutamist ja maksumust Eestis *sclerosis multiplex*'i bioloogilise ravi näitel. Uurida, kuidas ja millise kvaliteediga esinevad andmed erinevates andmebaasides ning kas andmete süntees võimaldab tervikpilti bioloogilisest ravist ühe diagnoosi raames.

Meetod: Tehti kindlaks, millist bioloogilist ravi kasutatakse *sclerosis multiplex*'i raviks, erinevatest andmebaasidest koguti andmed *sclerosis multiplex*'i bioloogilise ravi kasutamise ja kulude kohta ning vastavate andmebaaside andmeid võrreldi. Kasutati järgmisi andmebaase: Ravimiamet (kasutab andmete avaldamise kanalina Tervise Arengu Instituudi Tervisestatistika ja terviseuuringute andmebaasi), Eesti Haigekassa, haiglate andmebaasid. Uuriti, millised on bioloogilise ravi kasutamise ja maksumuse arengusuunad erinevate klassifikatsioonide kaupa.

Tulemused: Bioloogilise ravi kasutus suureneb igal aastal. Tulemuste põhjal näeb trendi, mille põhjal ajalooliselt vanemate ning odavama hinnaga bioloogiliste ravimite (interferoonid) kasutus ajas väheneb ning uuema põlvkonna ja kallima hinnaga ravimite (peamiselt monoklonaalsed antikehad) kasutus ajas suureneb.

Kokkuvõte: Erinevate andmebaaside andmeid analüüsides ning võrreldes on võimalik näha kindlaid trende, kuid olenemata sellest, et erinevad andmebaasid pakuvad mitmekülgseid andmeid, ei võimalda andmebaaside erinevad piirangud terviklikku pilti moodustada ning tulemused on kohati eksitavad.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 78 leheküljel, 6 peatükki, 24 joonist, 7 tabelit.

List of abbreviations and terms

ATC	Anatomical Therapeutic Chemical Classification System
BRM	biological response modifier
CNS	central nervous system
DDD	defined daily dose
EHIF	Estonian Health Insurance Fund
IFN	interferon
IL	interleukin
IM	intramuscular
IV	intravenous
mAb	monoclonal antibody
mcg	microgram
mg	milligram
MS	multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAM	State Agency of Medicines
SC	subcutaneous
TUT	Tallinn University of Technology
WHO	World Health Organization

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1 Introduction

New technologies applied by pharmaceutical industry have expanded opportunities for treating of many diseases and which affects the efficacy of treatment significantly. Application of new technologies have led to development of highly specific biological treatments with high efficacy. On the other hand, these new treatment opportunities change also the management of health care enormously.

Biological treatment is increasingly used and has successfully proven its efficacy for treating many chronic and life-threatening illnesses. The importance and use of biological treatment is continuously increasing due to new technological advances enabling development of new approaches for biological treatments. Also, biological treatments spread to new disease groups where there was no treatment previously.

If biological treatment is started on a patient in proper time, it eventually leads to cost savings as it might eliminate the risks of surgical interventions, improves work ability etc [2].

The cost of biological treatment also depends on indirect non-drug costs such as route of administration [46] and hospital stays [2]. Taking all these aspects into consideration, it is very complicated to analyse direct and the associated in-direct costs of biological treatment. Understanding the trends of usage and cost of this treatment provides some insight on these aspects.

For multiple sclerosis, there are currently many biological treatments available in Estonia that are reimbursed by the Estonian Health Insurance Fund. These treatments involve the usage of both historically older biological treatments (interferons) and newer generation therapies (monoclonal antibodies). MS biological treatment is reimbursed in Estonia via different pathways by the health insurance.

All these developments of pharmaceutical industry implicate serious changes for health care system ethically and financially and managing the comprehension of this specific treatment creates challenges in health care.

2 Background

2.1 Definition and classification of biological treatment

Biological treatment (also called bio- or immunotherapy) is a type of treatment that induces, enhances or suppresses the body's immune system. It is intended to influence body's natural immune system to treat or modify the course of a disease. Biological treatment involves the usage of substances called biological response modifiers (BRMs), such as interferons, interleukins, tumour necrosis factor, monoclonal antibodies, colony stimulating factors and cancer vaccines [3]. Using contemporary biotechnological techniques, BRMs as biological agents can be produced in large amounts. BRMs are most commonly used for treating cancer, rheumatoid arthritis, Crohn's disease, multiple sclerosis (MS) and many other diseases. Biological treatment can be administered orally, intravenously or as an intramuscular or subcutaneous injection. Although there are many types of biological treatments including immunotherapies like cancer vaccines, oncolytic virus therapy, T-cell therapy etc., most of the new generation biological treatments are monoclonal antibodies [1].

Biological treatment that provokes or enhances the immune system is called activating biological treatment and biological treatment suppressing immune system is called suppressive biological treatment [44].

2.2 Immunological background

Biological pharmaceuticals are biotechnologically produced by living organisms or substances derived from them and stimulate body's immune response by acting against different and specific targets [35].

The adaptive, or acquired immune system consists of two main types of lymphocytes: T and B lymphocytes (also called T and B cells) [42]. These cells play the central role in the adaptive immune system response. B lymphocyte's major function is to produce antibodies that recognize antigens and to help eliminate invaders. T lymphocytes help to destroy threats to the body. Cytokines, predominantly produced by T-cells, are proteins

involved in the body's inflammatory reactions, having a specific effect on communication and interactions between cells [10], [47].

BRMs in biological treatment are tools for stimulating different body's defence mechanisms, for example, monoclonal antibodies in MS target specific cells that attack nerve cells, cytokines (interferons and interleukins) alter directly or indirectly immune response and inflammatory reactions in MS by targeting and regulating cytokine signalling pathways [10], [44].

2.3 Non-specific immunological biological treatment

Common non-specific immunotherapies are interferons and interleukins.

Interferons (INFs) are cytokines that mediate antiviral, antiproliferative and immunomodulatory activities. INF are cytokines produced by the immune cells in response to viral infections and cytokines, promoting T-cell immune response. Three major classes of human IFNs are alpha, beta and gamma [3].

Interleukins (ILs), are cytokines produced by lymphocytes that elicit complex immunomodulatory functions including cell proliferation, migration, adhesion and maturation [6].

2.4 Monoclonal antibodies

Monoclonal antibodies (mAbs) are antibodies produced by a single clone of B cells. Biotechnologically mAbs are homogenous and monospecific drugs and effective tools for developing therapies and diagnostics [4].

In 1975 Cambridge biochemists George Köhler and Cesar Milstein presented a new technique, now called the hybridoma technique that allows to produce large amounts of monoclonal antibodies with predefined specificity. This principle was discovered by merging antibody-producing B-cells with myeloma cells. MAbs act directly against specific antigens. Each B cell produces a single type of antibody hence can bind to only one type of antigen and they can be immortalized (capable of indefinite growth in vitro) into immunoglobulin-secreting in vitro cell lines [28], [36].

The development of mAbs started with production of mouse cell based mAb, mouse to mouse-human chimeras, and later to humanized mAb. MAbs are identical copies of naturally occurring antibodies but are artificially produced by a genetic engineering technique [36].

MAbs are homogeneous, directed against single epitopes, highly specific and can be produced in limitless quantities, therefore extremely useful for identification and antigenic characterization of pathogens. MAbs have enormous applications in the field of therapeutics, diagnostics and targeted drug delivery systems. Their therapeutic strategy involves having effect on infectious diseases caused by bacteria, viruses, also cancer, metabolic and hormonal disorders, including inhibition of alloimmune and autoimmune reactivity [38], [4].

An example of a monoclonal antibody's mechanism of action is illustrated in Figure 1. Lymphocytes are able to infiltrate in the blood-brain barrier in MS patients. A monoclonal antibody natalizumab blocks the lymphocyte entry into the central nervous system (CNS) [39].

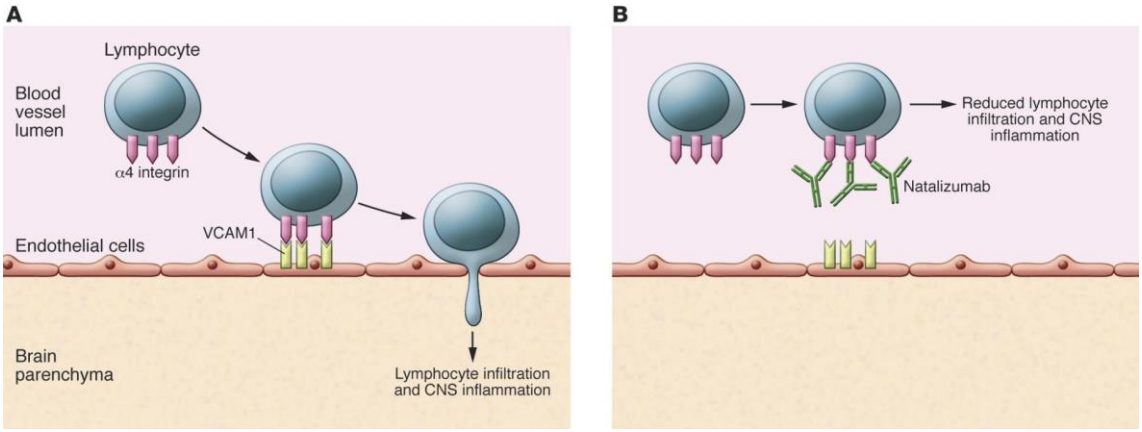

Figure 1. Lymphocyte infiltration in the blood-brain barrier in MS blocked by a monoclonal antibody.

International Non-proprietary Name (INN) Expert Group/WHO Expert Committee on Specifications for Pharmaceutical Preparations established by WHO has developed rules for names of pharmaceutical preparations. According to INN suggestion, any mAb name consists of a prefix, a substem A, a substem B and a suffix. A suffix for mAb has been assigned *-mab*, which indicates that these products embody an immunoglobulin variable domain which binds to a specific target. Substem B illustrates the species of origin [27].

Table 1. Substem B of monoclonal antibodies INN.

Substem B	**Species of origin**
-a-	rat
-axo-	rat-mouse
-e-	hamster
-i-	primate
-o-	mouse
-u-	human
-vet-	veterinary use
-xi-	chimeric
-xizu-	chimeric-humanized
-zu-	humanized

2.5 Oral targeted biological treatment

The mode of administration of biological treatments is different and reimbursement method may depend on mode of administration. Medications may be reimbursed under the medical or pharmacy benefit. Biological treatment that requires frequent oral administration is usually classified as oral targeted treatment and the reimbursement is prescription/pharmacy based [37].

2.6 Indications of biological treatment

Biological treatment is indicated for a wide spectrum of diseases. The most common biologic medications, mAbs are widely used for autoimmune and infections diseases, malignancies and also transplant rejection [25].

In oncology, biological treatment for cancer is often linked with conventional treatment such as surgery, chemotherapy and radiotherapy. Biological treatment is used for different types of cancer, for example breast cancer, melanoma, metastatic colorectal cancer, Non-Hodgkin lymphoma and many others [3], [32].

Biological treatment is also indicated for many chronic inflammatory and autoimmune diseases such as psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic

arthritis, systemic lupus erythematosus, ankylosing spondylitis, inflammatory bowel diseases (ulcerative colitis, Crohn's disease), systemic sclerosis, multiple sclerosis [30], asthma and inflammatory pulmonary diseases [45].

2.7 Side effects of biological treatment

BRMs can lead to some side effects, depending on the type of treatment. Side effects of biological treatment are frequently target-related and associated with their biological outcomes of their direct action. The targets of these biological agents are simultaneously components of several natural processes of physiology [31]. Side effects usually decrease in intensity during treatment and after the treatment [29]. Different treatment options should be considered before starting biological treatment [8].

Cytokines, regardless of being a group of proteins produced by the immune system itself, have the potency of causing adverse effects on patients. This treatment often causes flu-like symptoms (fatigue, fever, nausea, chills, vomiting), injection-site and infusion reactions and gastrointestinal effects may occur [3], [29]. Furthermore, particularly IL-2 can cause rash or swelling, and treatment with higher doses can lead to blood and kidney toxicites, low blood pressure and pulmonary edema [5]. An oral targeted medication fingolimod has a cardiovascular side effect as it decreases heart rate and causes arrythmias [44], it can also cause macular oedema [33]. Adverse events of administrating mAbs are diverse and can result in immune reactions like serum sickness, anaphylaxis and generation of antibodies. It can also cause organ-specific adverse effects such as cardiotoxicity [25].

2.8 Cost of biological treatment and previous studies

Biological treatment is innovative, highly effective and becoming more frequently used. On the other hand, this innovative treatment is available at a high cost, imposing an increasing financial burden on healthcare expenses [46].

In the United States of America (US), a research done by Shih *et al.* in 2015 demonstrated that the proportion of patients who received targeted intravenous (IV) anticancer medications grew from 9% to 28% during 2001 to 2011 and targeted oral anticancer

medications increased from 2% to 14% among nonelderly patients with cancer receiving chemotherapy during the same time-period. According to their findings, total drug expenditures for patients receiving targeted therapies were responsible for 63% of all chemotherapy expenditures in the US in 2011. Average insurance payments per patient within the first year of therapy was increased by 14 000 USD during the 10-year period. Majority of this increase was due to switching from classical chemotherapy to targeted agents. The distribution of nonelderly privately insured US cancer patients who underwent chemotherapy between January 1, 2001, and September 30, 2011, by type of chemotherapy agent, is illustrated in Figure 2 (IV = intravenous) [37].

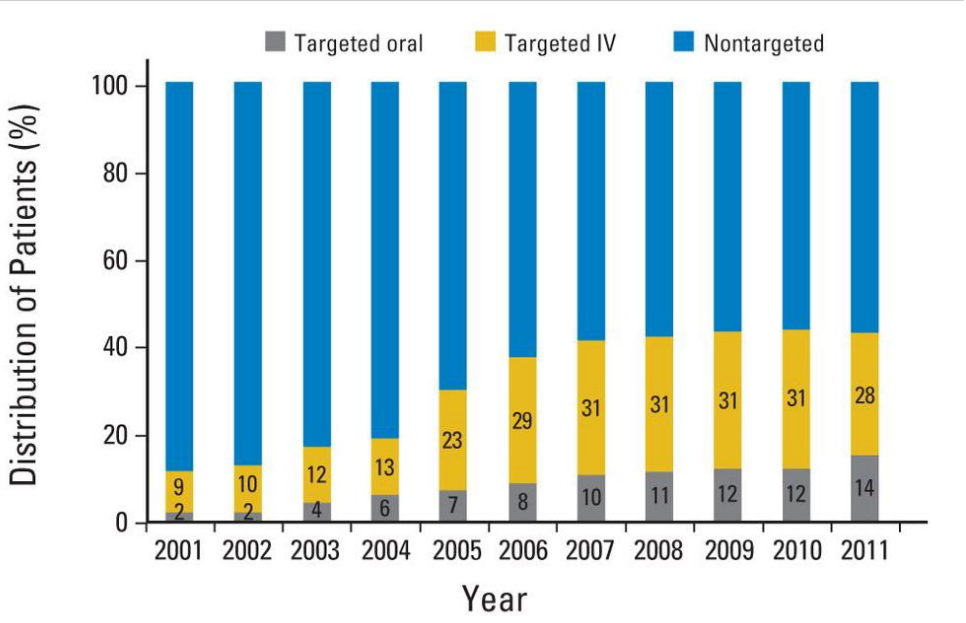

Figure 2. Distribution of chemotherapy agents used on US cancer patients from 2001–2011.

Another research about the cost of biological treatment was performed by Beck *et al.* in 2015 using Alsace health claims data from the DCIR (Données de Consommation Inter Régime) and PMSI (Programme de Médicalisation des Systèmes d'Information) databases. In this analysis, rheumatoid arthritis (RA) treatments were linked with any of the nine biological treatments available in France in 2012. The results demonstrated that 1075 patients of 5702 RA patients were receiving biological treatments in 2012. The overall cost of all RA treatments (5702 patients) in Alsace was 30.3 million euros in 2012. Further analysis indicated that the cost of treatment of those 1075 RA patients on biological treatments (18.85% of 5702 patients) was 14.9 million euros, comprising 49.2% of the total amount of RA treatment. This analysis demonstrates that while only

less than 20% of RA patients received biological treatments, they consumed almost half of total expenditures [2].

A landmark research was a study conducted in 2015 by Hartung *et al.* which aimed to investigate trends of cost of MS disease-modifying therapies (DMTs) in the USA. The authors examined the trends of costs of MS DMTs and the impact of new generation therapies arising and older therapy forms (first-generation therapies, interferons) usage decrease by computing the average annual acquisition costs for each month from July 1993 through December 2013 and they estimated acquisition costs using average wholesale price published by First DataBank. The study group discovered that the first-generation DMTs costs have increased over the years (from about $8 000 to $60 000 per year) and the price growth also increases prescription drug inflation. At the same time, market newcomers, the new generation DMTs arrive to markets with even higher price (20%–60% higher) than the existing older DMTs. For example, when arriving to the market in 2004, the cost of natalizumab as the first mAb for MS, was over 50% higher than interferon beta-1b, interferon beta-1a and glatiramer acetate. Similarly, fingolimod arrived at the market in 2010 with over 25% higher cost than first-generation DMTs. All in all, they suggest that the escalating costs of first-generation DMTs may be the reaction of newly-arrived and competitive therapies. The study group also compared the costs of MS medications in the USA to other countries. One of the reasons of the vast differences in costs is the fact that pharmaceutical companies are able to increase medication prices in the USA limitlessly since USA does not have national health care system and Medicare is not legally allowed to negotiate medication prices with the pharmaceutical industry. Table 2 represents the trends of costs (per patient per year) of biological treatments in the USA context as estimated acquisition costs using average wholesale price (AWP). Table 3 represents annual costs per patient of MS DMTs in the USA relative to cost estimates from other countries. Interestingly, private insurance system and the US Department of Veterans Affairs are allowed to negotiate pharmaceutical prices with the industry and this is reflected on the price of medication for them (table 3) [26].

Table 2. Market release date costs and annual costs per patient of 2013 of MS disease-modifying biological treatments in the USA.

Active substance	**US approval year**	**Approval date, annual cost $**	**2013 annual cost**	**Annualized change, %**
interferon beta 1-b (Betaseron)	1993	11 532	61 529	21.0
interferon beta 1-a (Avonex)	1996	8 723	62 394	34.6
glatiramer acetate (Copaxone)	1996	8 292	59 158	35.7
interferon beta 1-a (Rebif)	2002	15 262	66 394	28.1
natalizumab (Tysabri)	2004	25 850	64 233	16.2
interferon beta 1-b (Extavia)	2009	32 826	51 427	13.0
fingolimod (Gilenya)	2010	50 775	63 806	7.9
teriflunomide (Aubagio)	2012	47 651	57 553	16.8

Table 3. Annual costs of multiple sclerosis disease-modifying therapies in the United States relative to cost estimates from other countries.

Active subtance	**US Medicaid**	**US VA**	**Canada**	**Australia**	**UK**
interferon beta 1-b (Betaseron)	49 146	10 583	18 218	11 174	12 018
interferon beta 1-a (Avonex)	49 837	30 273	18 641	12 641	14 113
glatiramer acetate (Copaxone)	47 253	34 635	14 779	13 107	11 124
interferon beta 1-a (Rebif)	53 032	30 451	22 267	12 641	17 550
natalizumab (Tysabri)	51 306	36 485	33 651	22 505	22 510
interferon beta 1-b (Extavia)	41 078	22 821	16 456	11 174	12 018
fingolimod (Gilenya)	50 965	41 269	28 287	27 742	31 810
teriflunomide (Aubagio)	45 970	35 357	price pending at the time of the study	22 154	22 458

2.8.1 Mode of administration and cost

In 2016, Yokomizo *et al.* published a study investigating cost-effectiveness of different biological treatments used in moderate-to-severe ulcerative colitis. The study group constructed a decision tree based on a payer perspective and retrieved the costs of adalimumab, infliximab and vedolizumab from Medicare reimbursement rates and wholesale medication prices in the USA. The authors analysis also included both drug and administration costs of biological treatments. The study demonstrated that the cost-effectiveness of biological treatments depends also on the route of administration. They discovered that infliximab, biological agent that is administered via intravenous infusion (IV) produce non-drug costs (mainly drug administration costs) that can be even greater than the cost of the medication itself. They concluded that infliximab was the most cost-effective of the three biological treatments only if costs of the medication administration are not excessive (less than $2000). According to their data, for instance, adalimumab with almost no non-drug costs (administered subcutaneously), is considered to be more cost-effective biological treatment than infliximab in case infliximab's non-drug costs are high [46].

Similar data was demonstrated in a research done by Beck *et al.* for biological treatment of RA. In RA treatment, about 10 million euros in 2012 were spent on biological medications and 2.4 million euros in addition on in-patient care necessary for the delivery of biological treatments [2].

Reimbursement mechanisms of biological treatments frequently depend on the route of administration leading to different compensation pathways, under the medical or pharmacy benefit (Shih et al., 2015). Also, dosing schedules are widely different from isolated treatments courses to permanent treatments. In addition, patients may need switching between therapies [2].

In conclusion, for administrators and health care budget planners it is extremely complicated to predict the costs of managing diseases that can be treated using biological treatment.

2.9 Biological treatment compensation mechanisms in Estonia

Estonian Health Insurance Fund (EHIF) is the major institution providing medical coverage in Estonia. There are mainly two different reimbursement mechanisms for pharmaceuticals (including biological treatment): reimbursement based on list of medicinal products (pharmacy based reimbursement) and list of health care services (medical reimbursement).

2.9.1 List of medicinal products

EHIF compensates medicinal products that are included in the EHIF's list of medicinal products and registered in Estonia (pharmacy-based reimbursement). Prescription pharmaceuticals are reimbursed according to specified list validated by the Ministry of Social Affairs. Prescription pharmaceuticals are compensated on the basis of diagnosis 50%, 75%, 90% or 100% of total cost of medications. The total cost depends on price agreements (in case they exist, if not, the refund will be based on the product's retail price). Prescription pharmaceuticals are issued from the pharmacy already with discounted price for patients and the treatment is home-based. Reimbursement of these products is an open commitment to the EHIF i.e EHIF is obliged to compensate all these products in the amount prescribed with pre-specified level of reference price without limitations. Therefore, lack of funds for instance cannot be a reason to limit the use of these medications [12], [15].

2.9.2 List of health care services

The list of health care services (medical reimbursement) consists of all medical services, procedures and medications provided at the hospital/medical centre either on out-patient or in-patient basis. Some pharmaceuticals used in hospitals are also reimbursed via health care services list. These „pharmaceutical treatments" are described in the services list with R-codes. Pharmaceutical treatments mainly represent chemotherapy in oncology and hematology, biological treatments and other specific expensive medicinal products [12].

The list represents the price of each service, procedure etc. and the specific conditions of payment. EHIF pays for the services in the list to the health care institution if the service is provided to the insured person on a medical indication. The prices are represented as maximum ceiling price, include capital costs and apply universally without any further provider-specific adjustments. However, all services are fully reimbursed to the medical

institution only if performed within the limits of the budget agreed beforehand with EHIF [14].

2.10 Biological treatment used in patients with multiple sclerosis

MS is a chronic neurological disorder affecting the brain and/or spinal cord of the nervous system and can sometimes cause serious disability. This long-lasting disease commonly begins in young adults thus treatment may be necessary for several decades. Currently there is no cure for MS. Options for the most common form of MS, relapsing remitting MS (RRMS), include oral targeted therapy, non-specific immune therapies (injectable therapies) and monoclonal antibodies. These therapeutics alter or suppress immune system, resulting in fewer and less severe relapses and slowing the course of MS [7].

It is believed that MS is driven by malfunctioning immune system that mistakenly attacks and damages the myelin sheath. With MS, lymphocytes and macrophages, that play a crucial role in immune system are able to break through the blood-brain barrier surrounding the blood vessels that protects central nervous system (CNS) and attack myelin. This creates inflammation in the CNS resulting in lesions with myelin damage. The best strategy to modify the disease course is to develop medications that target autoreactive immune cells [9]. Both T and B-cells are believed to be the key role players in MS pathogenesis and these are the appealing targets for therapeutic interventions [34]). Currently there are many therapeutics available for MS, including non-specific immunotherapy (interferons, glatiramer acetate), targeted oral medications, (dimethyl fumarate, teriflunomide, fingolimod), humanized monoclonal antibodies (natalizumab, alemtuzumab, ocrelizumab, ofatumumab, daclizumab) and emerging immune modulation approaches (stem cells, DNA vaccines, nanoparticles, altered peptide ligands) [9].

2.11 Biological treatment used in patients with multiple sclerosis in Estonia

Biological treatment used in Estonia for patients with MS that are reimbursed by the Estonian Health Insurance Fund are illustrated in Table 4 according to their ATC (Anatomical Therapeutic Classification System), reimbursement list and routes of administration (IM = intramuscular, SC = subcutaneous, IV = infusion) [11].

Table 4. Biological treatment used in Estonia for patients with multiple sclerosis.

ATC	**Active substance**	**Brand name**	**Reimbursement list**	**Route of administration**
L03AB07	Interferon beta-1a	Avonex, Rebif	Medicinal products	IM, SC
L03AB08	Interferon beta-1b	Betaferon, Extavia	Medicinal products	SC
L03AB13	Peginterferon beta-1a	Plegridy	Medicinal products	SC
L03AX13	Glatiramer acetate	Copaxone	Medicinal products	SC
L04AA31	Teriflunomide	Aubagio	Medicinal products	Oral
L04AA23	Natalizumab	Tysabri	Health care services (code 346R)	IV
L04AA27	Fingolimod	Gilenya	Health care services (code 346R)	Oral
L04AA34	Alemtuzumab	Lemtrada	Health care services (code 349R)	IV

Mechanisms of actions and indications are represented in Appendix 2.

3 Research methodology

1.1 Research objectives, questions and hypotheses

The objective of this research is to analyse the quality and availability of information on biological treatments in Estonia. Biological treatment of multiple sclerosis (MS) as a model was selected as an example. In MS field there have been made significant recent advances in biological treatments.

The aim is to develop a model for analysis of usage, cost and need of biological treatments. This research collects and analyses data about usage and cost of biological treatments used in patients with MS among Estonian population and compares availability and quality of data of these medications between different databases.

Research questions:

- What is the usage and trends of different biological treatments in multiple sclerosis?
- Is the available data of biological treatments compatible/cumulative/additive in different databases creating a comprehensive overview of usage?
- What is the cost of biological treatment of multiple sclerosis?
- How to predict the cost of biological treatments in the future?

Research hypothesis:

- Biological treatments of interest are categorized according to their mechanism (mode) of action (MoA)
- Data of usage and cost of biological treatments is scattered and varied in different databases, but provides a broad and comprehensive overview if all the pertinent data is collected

- Analysis of data of pharmaceuticals that are used in very small amounts is inaccurate in State Agency of Medicines data channel but can be traced through health insurance database
- The usage and cost of biological treatment of patients with multiple sclerosis has increased in Estonia
- The need of biological treatments surpasses the availability for patients with multiple sclerosis
- Analysis of usage and cost of biological treatment is feasible, predicting the actual need is complicated

3.1 Research method and databases

The definition of biological treatment is that they are medications using BRMs resulting in inducing, enhancing or suppressing the body's immune system. These medications are mainly classified in Anatomical Therapeutic Classification System (ATC system) as ATC-L (Antineoplastic and immunomodulating agents) classification and reimbursed in Estonia mainly via two pathways: through the list of medicinal products and list of health care services.

This thesis is synthesing and comparing data mainly from the following databases:

1. State Agency of Medicines
2. Estonian Health Insurance Fund database (prescription database [13] and list of health care services database)
3. Databases of all hospitals providing biological treatments for MS

Population data is retrieved from Statistics Estonia database.

All data was derived as non-personalized data.

The author of this thesis did a research about which medications and active substances are used in Estonia for MS biological treatment [11] and the results are presented in Table 4.

Table 4. Biological treatment used in Estonia for patients with multiple sclerosis.

ATC	Active substance	Brand name	Reimbursement list	Route of administration
L03AB07	Interferon beta-1a	Avonex, Rebif	Medicinal products	IM, SC
L03AB08	Interferon beta-1b	Betaferon, Extavia	Medicinal products	SC
L03AB13	Peginterferon beta-1a	Plegridy	Medicinal products	SC
L03AX13	Glatiramer acetate	Copaxone	Medicinal products	SC
L04AA31	Teriflunomide	Aubagio	Medicinal products	Oral
L04AA23	Natalizumab	Tysabri	Health care services (code 346R)	IV
L04AA27	Fingolimod	Gilenya	Health care services (code 346R)	Oral
L04AA34	Alemtuzumab	Lemtrada	Health care services (code 349R)	IV

3.1.1 State Agency of Medicines database

Most of the State Agency of Medicines data used in this thesis is derived from the State Agency of Medicines data channel, National Institute for Health Development Health Statistics and Health Research database (hereinafter referred to as SAM data channel). Additional data (sold quantities in grams of some particular active substances) was enquired specially via e-mail directly from the State Agency of Medicines (hereinafter referred to as State Agency of Medicines as a source, SAM2).

According to data available in the SAM data channel statistics on active substances purchased among ATC L-classification in Estonia are presented in Appendix 5 (Table 7). All active substances used for patients with MS in Estonia are represented under ATC L-classification.

State Agency of Medicines data channel, using the State Agency of Medicines as a source, provides statistics about medicine consumption based on the volume of sales to general and hospital pharmacies and other institutions (scientific and state institutions) by Estonian wholesalers' reports. The data is provided as the number of defined daily doses (DDD) per thousand inhabitants per day (DDD/1000 inhabitants/day) and categorized according to the ATC classification. According to definition set by WHO, DDD is "a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose" [43]. At the time of data derivation for this thesis, the data in this data channel was available for 2012–2016. Medication consumption statistics for the year 2017 in DDD/1000 inhabitants/day was available only on the official website of State Agency of Medicines.

State Agency of Medicines data channel does not differentiate between different medications that are produced with the same active substance. For example, interferon beta-1a is an active substance for two distinct (non-identical) MS medications: Avonex and Rebif. These medications cannot be statistically differentiated in State Agency of Medicines data channel. The same applies for interferon beta-1b: there are two MS medications produced with the same active substance: Betaferon and Extavia (identical). Also, glatiramer acetate's brand Copaxone is available in two different dosages (20 mg/ml and 40 mg/ml) with different administration frequencies. The differentiation of same medications with different doses is also not possible in the State Agency of Medicines data channel.

3.1.2 Estonian Health Insurance Fund database

The author of this thesis analysed which active substances are compensated according to which reimbursement pathway by EHIF (Table 4).

This research derived information from both the EHIF's prescription database (medicinal products database) [13] (pharmacy based reimbursement) and enquired data about health care services list (medical services based reimbursement list) from an EHIF data analyst via e-mail.

The data about usage and cost of pharmaceuticals compensated via list of medicinal products is available on the official website of the Estonian Health Insurance Fund. The medications are categorized for each year by their discount rate (0%, 50%, 75%, 90%,

100%), including diagnoses that are implicative of compensation, ATC codes, active substances, brand names, individual number of patients prescribed a particular brand of medication and individual number of patients prescribed a particular active substance, number of prescriptions, number of originals, total cost of prescription and amount remunerated by the EHIF.

The author of this thesis separately enquired data from the Estonian Health Insurance Fund about biological treatment reimbursed via „hospital pharmaceuticals" compensation mechanism. This type of treatment is coded as R-codes in the list of health care services (medical services reimbursement). The data received from EHIF counted the amount of each R-code compensated per each year, total number of patients who received each R-code service and also individual non-personalized data about every single patient who received treatment during this time period. R-code services in the health care list that are used for patients with MS are 346R (intended for reimbursing both natalizumab and fingolimod) and 349R (intended only for reimbursing alemtuzumab).

During the process of enquiring health care services data from the Estonian Health Insurance Fund, the data analyst explained that some codes allow to use different pharmaceuticals and EHIF does not intervene which medication should be used. The code for MS treatments 346R allows indeed the of use different pharmaceuticals. Thus, EHIF does not collect data which medication exactly was administered under code 346R. Therefore, it is not possible to determine the usage and cost of natalizumab and fingolimod from the EHIF database separately.

3.1.3 Hospital database

Hospital databases were utilized for comparing active substances used in very small amounts. Also, hospital database was the source to differentiate between medications coded under 346R code in EHIF database (fingolimod, natalizumab).

Also, only hospital databases were informative for an active substance called alemtuzumab which is a pulsed therapy. The problems with analysis of pulsed therapies originates from the fact that during the first year of treatment, a patient receives 5 vials (1 vial per day, 5 days in a row) and second year 3 vials of alemtuzumab (1 vial per day, 3 days in a row) [21]. Treatment volume per year is different for each patient depending on which course the patient is receiving treatment. It is impossible to calculate the costs of

alemtuzumab by using DDD units since it is not possible to evaluate the duration of treatment per patient per year (could be either 5 vials per year or 3 vials per year). Hence the only source of accurate information on pulsed therapy can be derived from hospital database. Information from hospital databases providing biological treatments was enquired via e-mail from Dr. Katrin Gross-Paju, Head of Neurology clinic, West Tallinn Central Hospital. She is also the liaison person for MS treatments between EHIF and Estonian Neurologists Association.

3.2 Specialists' perspective and interviews

Interviews about analysing and predicting the need of treatments were conducted with:

- Erki Laidmäe, Head of Division of Medicines and Medical Devices, EHIF
- Dr. Katrin Gross-Paju, Head of Neurology clinic of West Tallinn Central Hospital

Discussion with experts is provided in the results chapter of this thesis.

3.3 Synthesis and comparison of data

Databases have different approaches to categorize medications. Definition and classification of biological treatments is scattered and ambiguous. Also, these categorizations do not determine indication/diagnosis. In addition, mode of action cannot be determined from available classifications. Consequently, a prerequisite to determine which medications will be analysed as biological treatments is the pre-existing knowledge of a researcher what medications and what modes of actions are specific for the group of medications of interest before starting the study.

Fundamentally, analysing biological medications, a researcher has to know precisely which medications are relevant in the analysis, how are they classified in different systems and how are they used for certain disease(s). This is the only way to select medications that are in accordance with his or her scope of interest.

Since there is no generally accepted categorization in the databases, the author of this thesis chose to categorize MS biological treatment according to medications reimbursement pathway (list of medicinal products and list of health care services) and

proposes an additional categorization of MS biological treatment according to literature as following: oral targeted, non-specific immunological, monoclonal antibodies (table 5).

Table 5. Categorization of MS biological treatment in this thesis.

Oral targeted immunomodulatory	**Nonspecific immunological**	**Monoclonal antibodies**
L04AA31: teriflunomide	L03AB07: interferon beta-1a	L04AA23: natalizumab
L04AA27: fingolimod	L03AB08: interferon beta-1b	L04AA34: alemtuzumab
	L03AB13: peginterferon beta-1a	
	L03AX13: glatiramer acetate	

Each active substance used for patients with MS in Estonia was analysed by its usage and cost based on data from SAM database and EHIF database in the timeframe of 2012–2017. Most of the graphs were made separately as follows:

- Usage and cost based on SAM database:
    - Active substances categorized according to three groups of medications
    - Active substances categorized according to reimbursement pathway
- Usage and cost based on EHIF database:
    - Active substances categorized according to reimbursement pathway (not possible to categorize EHIF data according to three groups of medications since EHIF does not have distinguisable data of natalizumab (monoclonal antibody) and fingolimod (oral targeted)
- Comparison of SAM and EHIF databases:
    - Active substances categorized according to reimbursement pathway (not possible to categorize EHIF data according to three groups of medications since EHIF does not have distinguisable data of fingolimod (oral targeted) and natalizumab (monoclonal antibody)

Additional analysis was done using the hospital databases and SAM database as a data source (instead of SAM data channel).

3.4 State Agency of Medicines data channel and DDDs

SAM data channel does not enable to distinguish between different medications that are classified under the same active substance, for example interferon beta-1a formulations medication brands are Avonex and Rebif. The fixed DDD of interferon beta-1a is 4.3 mcg [43]). DDD 4.3 mcg corresponds accurately to Avonex. The actual daily dose of Rebif is 18.9 mcg (patients use 44 mcg of medication three times per week, so 132 mcg in total per week, 132/7=18.9 mcg per day), So, the DDD 4.3 mcg is not applicable for Rebif as its actual daily dose 18.9 mcg and the use of only this particular DDD (4.3 mcg) for the active substance of interferon beta 1-a confuses statistics. As a result, analysis of active substance interferon beta-1a done based on SAM data channel that uses only the DDD 4.3 mcg does not provide accurate results and the comparisons are meaningless. Due to inaccurate DDDs, analysis of SAM data mistakenly and artificially significantly increases the number of patients on this type of treatment.

The same statistical error applies to the usage of active substance glatiramer acetate. Different doses of the same medication are available: Copaxone 20 mg/ml and Copaxone 40 mg/ml). DDD for glatiramer acetate is 20 mg [43] which corresponds to Copaxone 20 mg/ml. Meanwhile, the actual daily dose of Copaxone 40 mg/ml is 17.1 (patients use 40 mg of medication three times per week, so 120 mg in total per week, 120/7=17.1 mg per day). Therefore, artificially the number of patients on these two medications is shown smaller (although all patients receive glatiramer acetate).

Unfortunately, there is no way how to differentiate the actual use of interferon beta-1a and different formulations of glatiramer acetate from SAM database.

The DDD calculations are accurate and correct for teriflunomide, peginterferon, interferon beta-1b since there are no different medications with different DDDs within the same active substance groups. Although, current classification does not differentiate between two identical brands (Betaferon, Extavia) of interferon beta-1b, but for current analysis perspective this is not important.

4 Results

Results of MS biological treatment usage and cost is categorized in this thesis according to:

1. three groups of medications (if possible) as specified in methods (table 5)
2. reimbursement pathway (list of medicinal products and list of health care services)

Reimbursement pathway of categorization was performed according to EHIF data. Non-specific immunologicals are all reimbursed through list of medicinal products (pharmacy based reimbursement), monoclonal antibodies are all reimbursed through health care services (hospital based medical services list). Oral targed medications may be reimbursed by either pathway.

4.1 Usage of biological treatment on multiple sclerosis patients based on State Agency of Medicines data channel

Medication consumption statistics in State Agency of Medicines (SAM) data channel is not categorized according to the proposed classification (see methods chapter), but according to active substances (table 7 in Appendix 5) and their ATC codes. All collected statistics is based on DDDs and depicted in table 6. Only since 2016 all MS biological treatment analysed became available in Estonia. DDDs of interferon beta-1a are significantly higher than for all other medications (overestimated) and glatiramer acetate's DDDs are underestimated. The statistical error is described in methods section.

Table 6. MS biological treatment consumption per year based on SAM data channel, expressed in DDD/1000 inhabitants/day. Please note that the numbers for interferon beta-1a and glatiramer acetate are misleading.

Active substance	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
L03AB07: interferon beta-1a	0.42	0.42	0.46	0.49	0.5	0.43
L03AB08: interferon beta-1b	0.1	0.1	0.1	0.1	0.09	0.09
L03AB13: peginterferon beta-1a	0	0	0	0	0.01	0.05
L03AX13: glatiramer acetate	0.09	0.12	0.14	0.13	0.14	0.14
L04AA23: natalizumab	0	0.01	0.02	0.02	0.02	0.02
L04AA27: fingolimod	0.01	0.01	0.01	0.02	0.02	0.02
L04AA31: teriflunomide	0	0	0	0.03	0.07	0.11
L04AA34: alemtuzumab	0	0	0	0	0.01	0.01

The numbers of MS biological treatment daily doses in 2012–2017 based on SAM data channel is represented on figures 3 and 4. All medications categorized to three groups (oral targeted immunomodulatory, nonspecific immunological medications and monoclonal antibodies) are depicted on figure 3. All medications categorized according to their reimbursement pathway (list of medicinal products and health care services) are shown on figure 4. The presented data demonstrates that the most used biological treatments according to different categorizations are non-specific immunological and medications reimbursed via list of medicinal products.

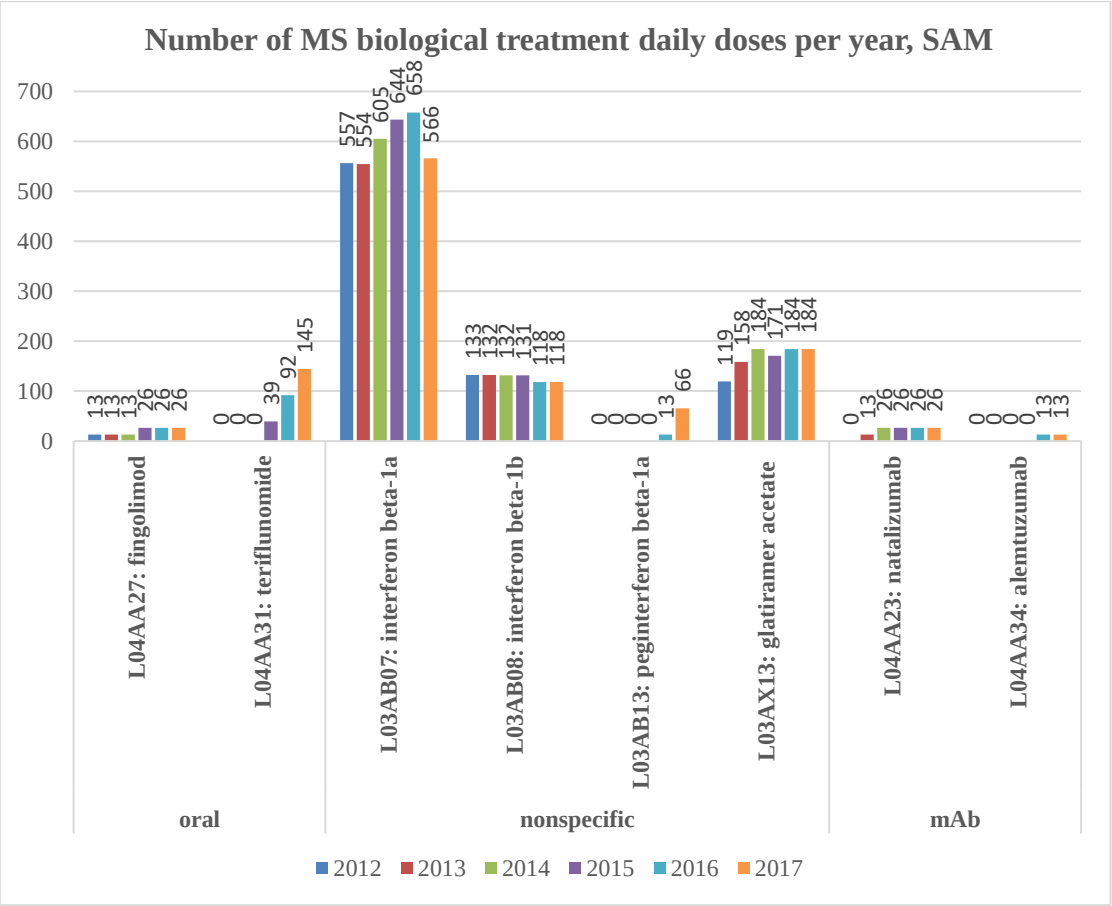

Figure 3. Number of MS biological treatment daily doses per year in 2012–2017 in Estonia according to SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

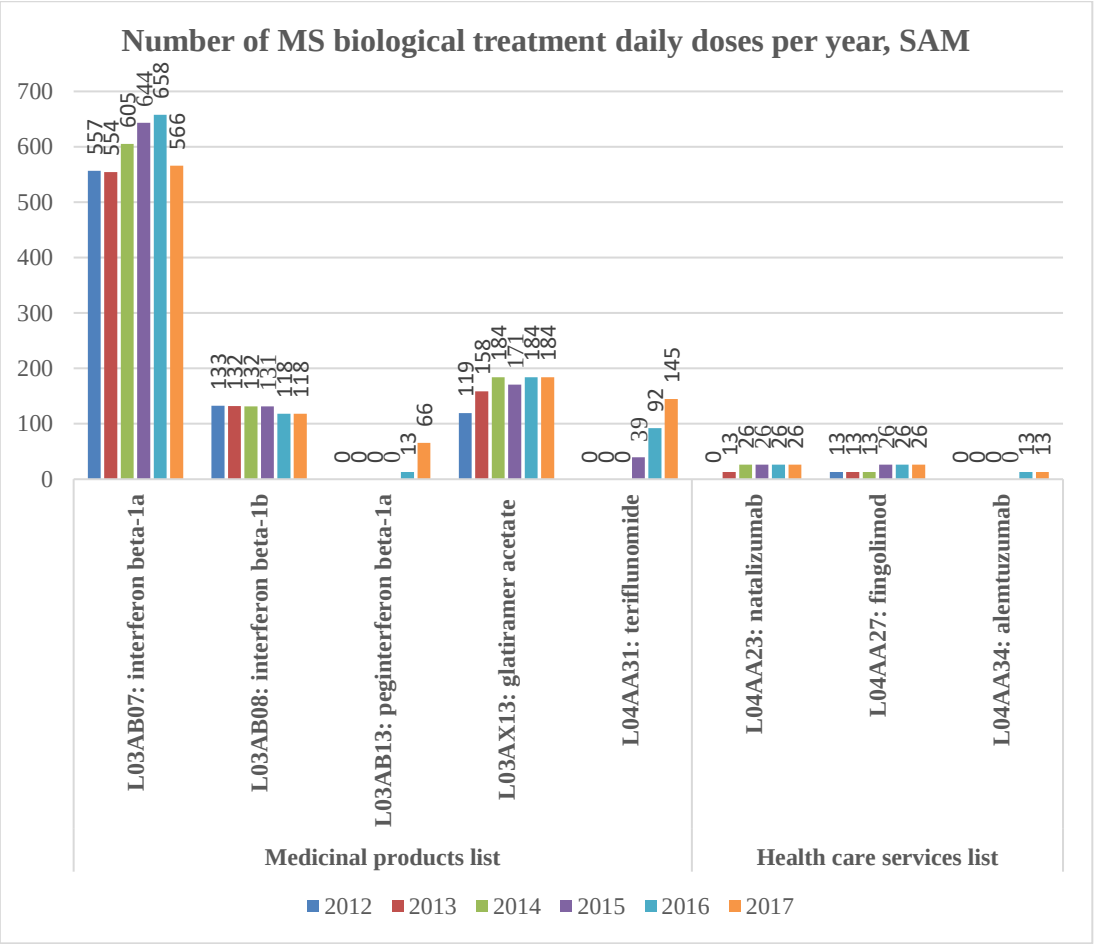

Figure 4. Number of MS biological treatment daily doses per year in 2012–2017 according to SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading

4.2 Usage of biological treatment on multiple sclerosis patients based on Estonian Health Insurance Fund data

EHIF database is not based on categorization of three groups (oral targeted immunomodulatory, nonspecific immunological and mAbs) of MS medications. The overview of usage of MS biological treatments in Estonia from 2012 to 2017 according to EHIF data is represented in figure 5. EHIF data demonstrates the number of patients on treatments individually and either reimbursed via list of medicinal products (pharmacy based reimbursement) or health care services list (medical services reimbursement). Figure 5 illustrates that vast majority of patients are receiving medications via medicinal services reimbursement pathway and only very few (77+9 in 2017) patients' treatment is reimbursed through medical services list. EHIF does not distinguish between natalizumab and fingolimod (both coded as 346R) but reports individually patients who have been

prescribed the same active substance but different medications, hence the usage of interferon beta 1-a and glatiramer acetate is differentiated in EHIF database.

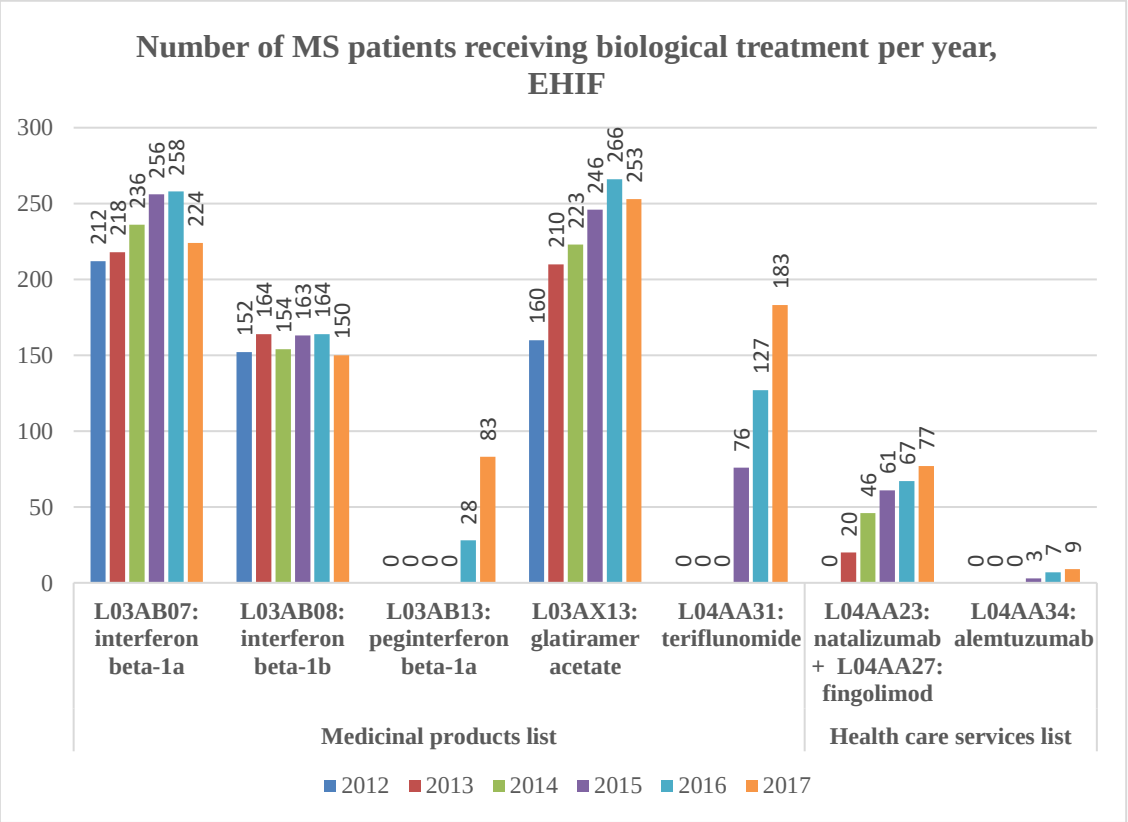

Figure 5. Number of patients receiving MS biological treatment based on EHIF database. Please note: interferon beta-1a takes account data both of Avonex and Rebif, interferon beta-1b both of Betaferon and Extavia, glatiramer acetate both of Copaxone 20 mg/ml and 40mg/ml.

4.3 Comparison of data of usage of multiple sclerosis biological treatment in Estonia

Comparison of data retrieved from both SAM data channel and EHIF database is represented in figure 6 for 2015–2017. Comparison for 2012–2014 is in the Appendix 1 in figure 17. Data on natalizumab and fingolimod is summed up (in all comparison graphs). Comparison of data from two databases proves the overestimation of interferon beta-1a usage and underestimation of usage of glatiramer acetate by SAM data channel. EHIF database on the other hand accounts for actual individual patients with at least one prescription per year.

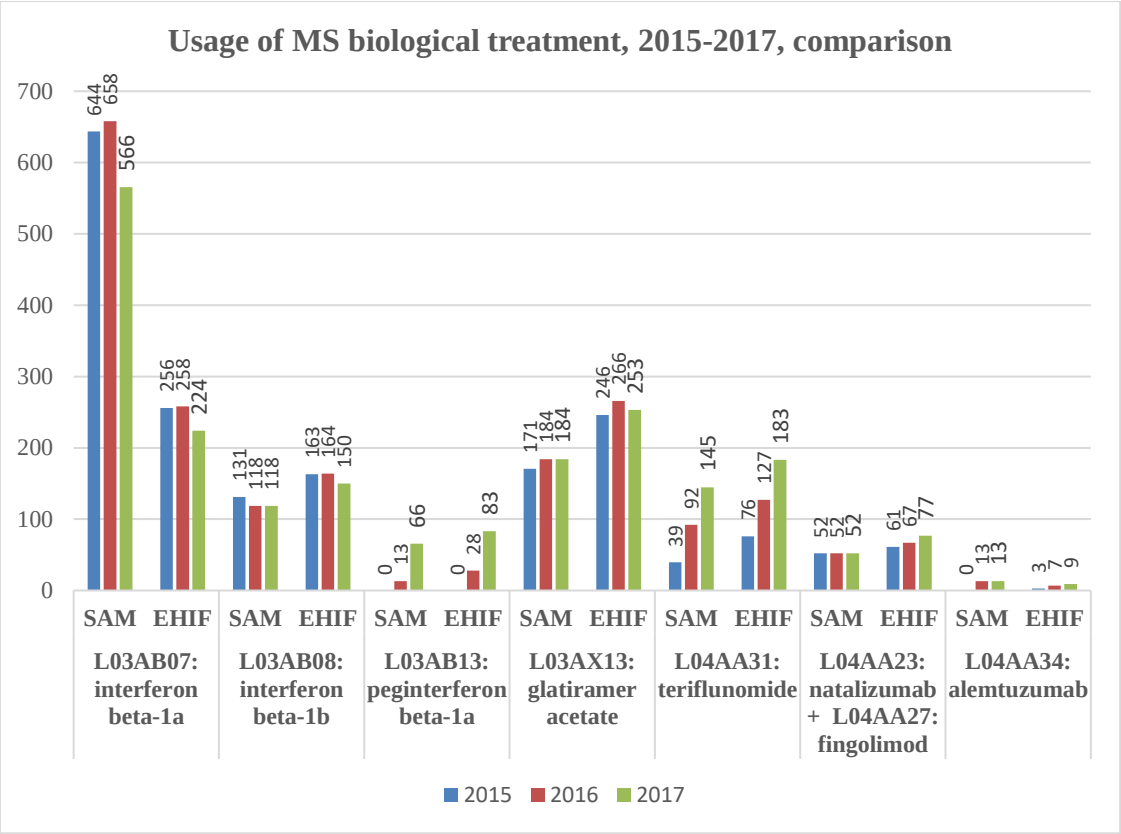

Figure 6. Usage of MS biological treatment per year in 2015–2017 in Estonia, comparison of databases. Please note that the calculations for interferon beta-1a and glatiramer acetate based on SAM channel are misleading.

4.4 Cost of biological treatment on multiple sclerosis patients based on State Agency of Medicines data channel

Cost of MS biological treatment per year based on SAM data channel categorized as three medication groups is represented in figure 7 and MS biological treatment categorized according to reimbursement pathway in figure 8. These figures do not include cost of alemtuzumab since it is pulsed therapy and it is not possible to calculate the cost of this medication based on DDD/1000 inhabitants/day. Since cost per year calculations are also based on DDDs provided by the SAM data channel, the same statistical error applies, leading to inaccurate reflection of the actual costs of interferon beta-1a and glatiramer acetate per year. Still it is clearly seen that the cost as well as usage of nonspecific immunological medications and medications reimbursed via list of medicinal products, prevails.

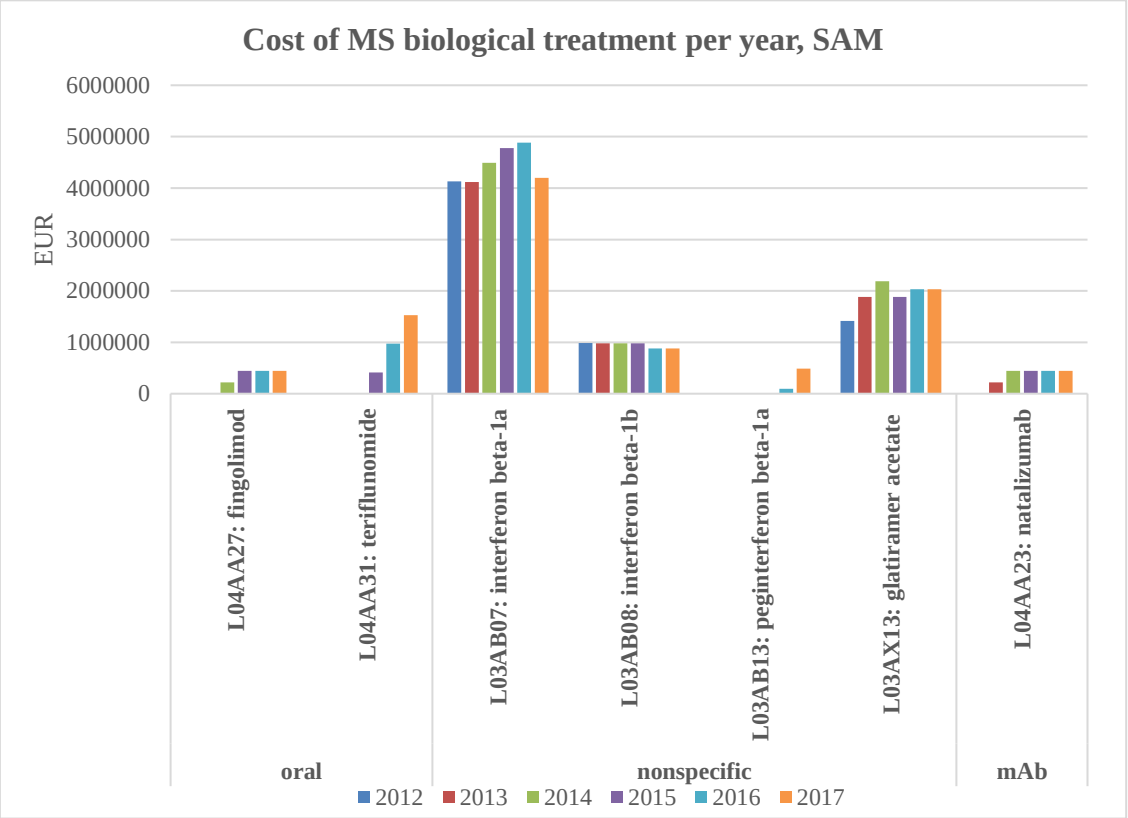

Figure 7. Cost of MS biological treatment per year based on SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

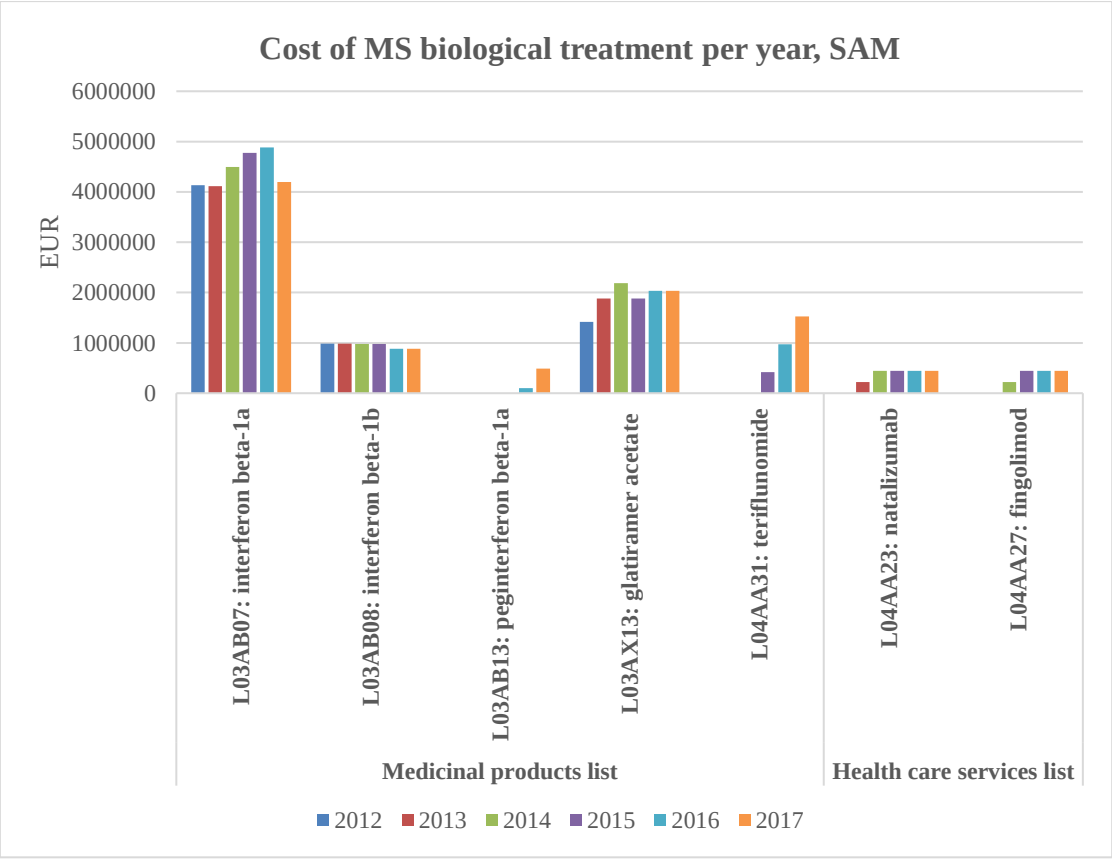

Figure 8. Cost of MS biological treatment per year based on SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

Cost of MS biological treatment per day per patient (which is used for basis for cost calculations with SAM data channel) categorized according to three medication groups is represented on figure 9 and according to reimbursement pathways on figure 10. The calculations for cost per day per patient are done based on reference prices and these results are not influenced by the statistical error of DDDs. The costs of medications reimbursed through medical services (hospital service reimbursement) are significantly higher than of medications reimbursed via pharmacy lists.

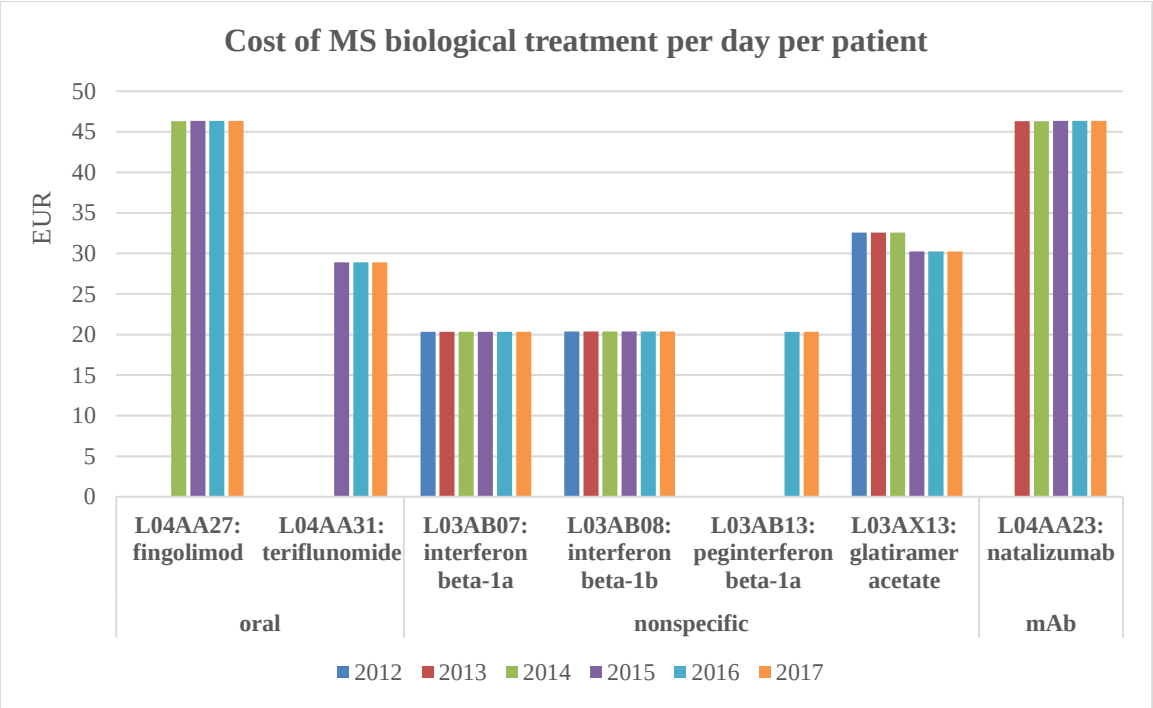

Figure 9. Cost of MS biological treatment per day per patient based on reference prices.

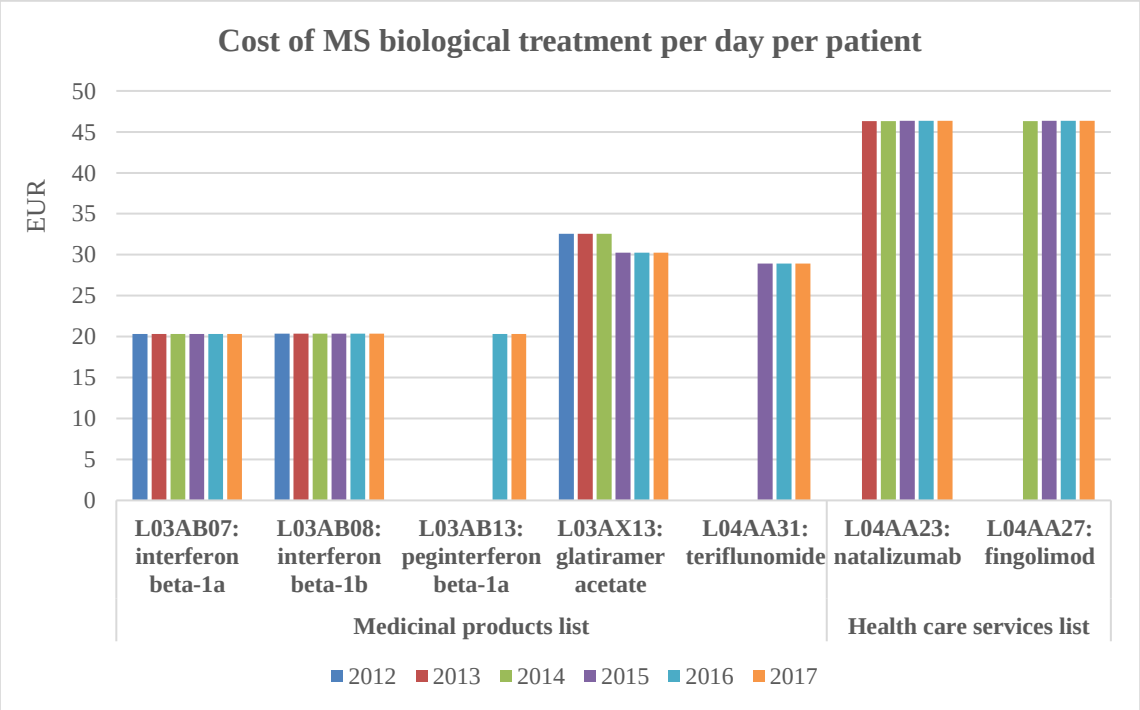

Figure 10. Cost of MS biological treatment per day per patient based on reference prices.

Cost of MS biological treatment per day per medication categorized according to three groups of medications based on SAM data channel is represented on figure 18 in Appendix 1 and according to reimbursement pathway in figure 19 also in Appendix 1.

Since cost per day per medication calculations are based on DDDs, these results are misleading. Collected data demonstrate that only daily cost of medications (according to reference price per patient) is a valid number to analyse costs.

4.5 Cost of biological treatment on multiple sclerosis patients based on Estonian Health Insurance Fund data

Cost of MS biological treatment per year based on EHIF database according to reimbursement pathways is represented in figure 11. These numbers are the actual amounts that EHIF has paid for MS biological treatment and it demonstrates the costs of medications reimbursed via list of medicinal products prevailing. However, the costs of non-specific immunological treatments (historically older generation treatments-interferons, glatiramer acetate) are slowly, but clearly decreasing. The costs of oral targeted (newer generation medicines - teriflunomide, fingolimod) and monoclonal antibodies (natalizumab, alemtuzumab) are increasing.

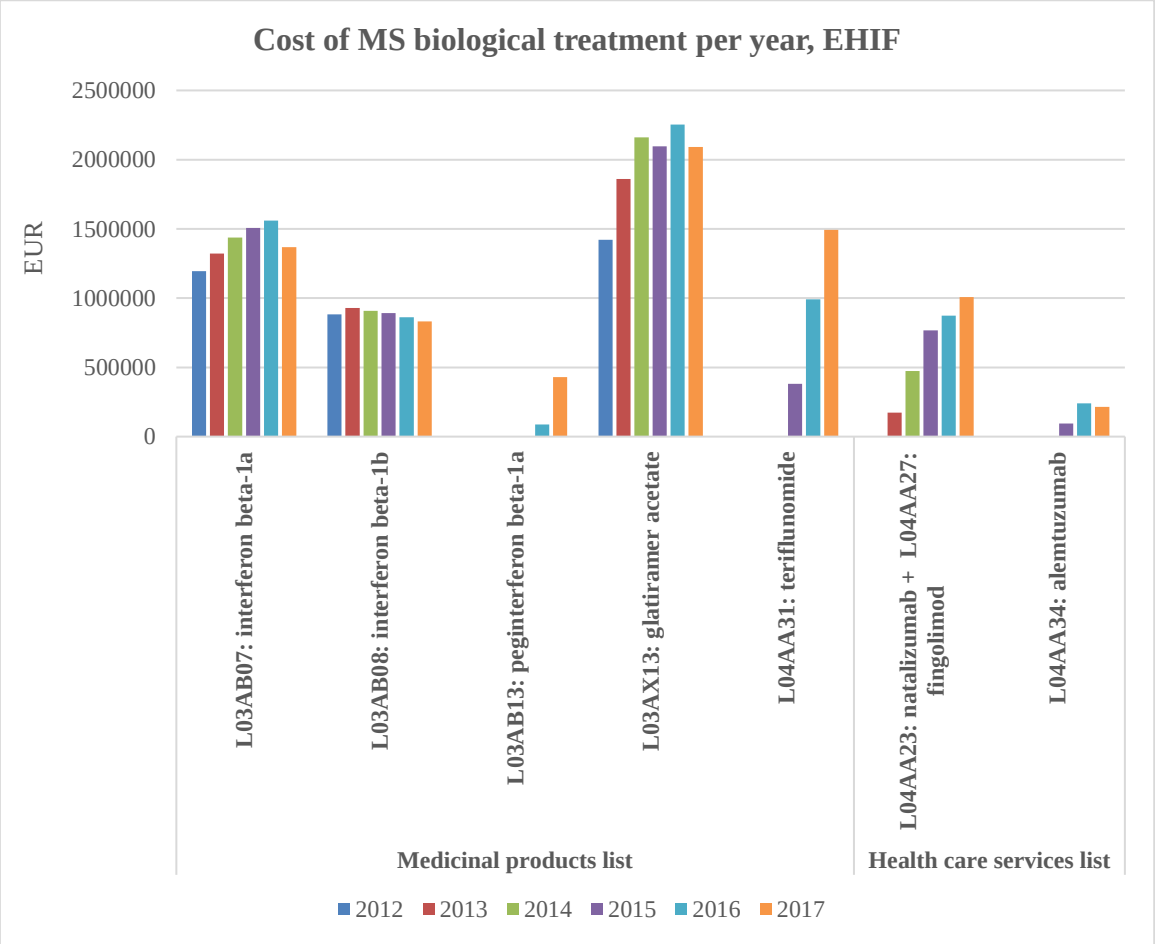

Figure 11. Cost of MS biological treatment per year based on EHIF database.

Cost of MS biological treatment per day per patient categorized according to reimbursement pathway based on EHIF data in represented in figure 12. Data demostrates that the costs per day per patient of medications reimbursed via list of health care services highly outperform the costs of medications included in the list of medicinal products.

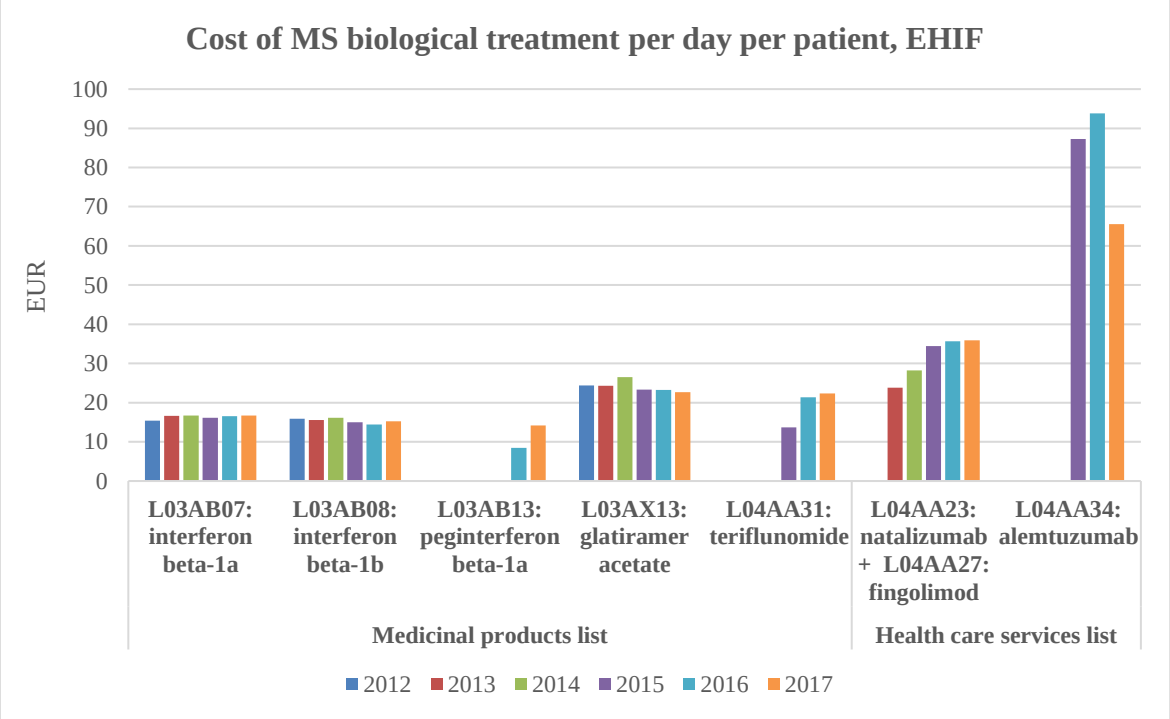

Figure 12. Cost of MS biological treatment per day per patient based on EHIF database.

Cost of MS biological treatment per day per medication categorized according to reimbursement pathway based on EHIF data is represented in figure 20 in Appendix 1.

4.6 Comparison of data of cost of multiple sclerosis biological treatment

Comparative graph of SAM data channel and EHIF database of MS medications cost per year in 2015–2017 is represented in figure 13. Figure 21 represents comparison of cost of MS biological treatment per year for 2012–2014 and is added to the Appendix 1. Again, it is shown how the statistical error of DDDs influences the results.

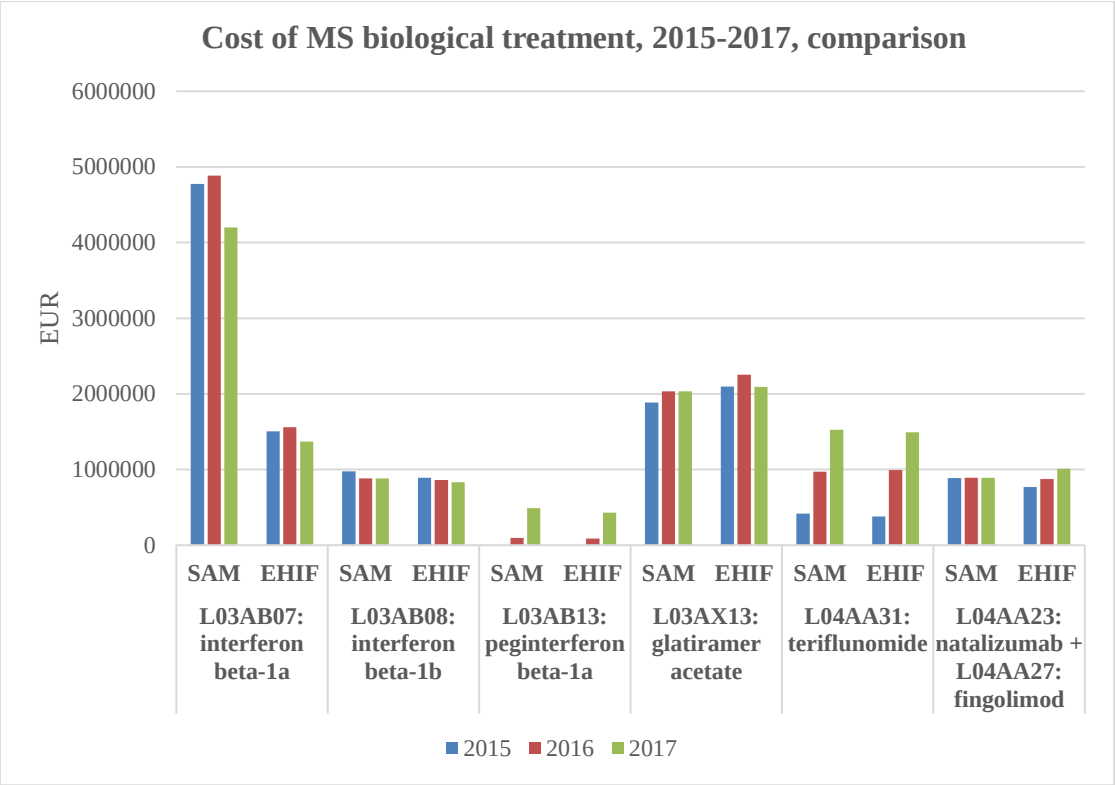

Figure 13. Cost of MS biological treatment per year in 2015–2017 in Estonia, comparison of databases. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

Comparison of cost of MS biological treatment per day per patient categorized according to reimbursement pathway in 2012–2014 is represented in figure 22 in Appendix 1 and 2015–2017 in figure 14 below.

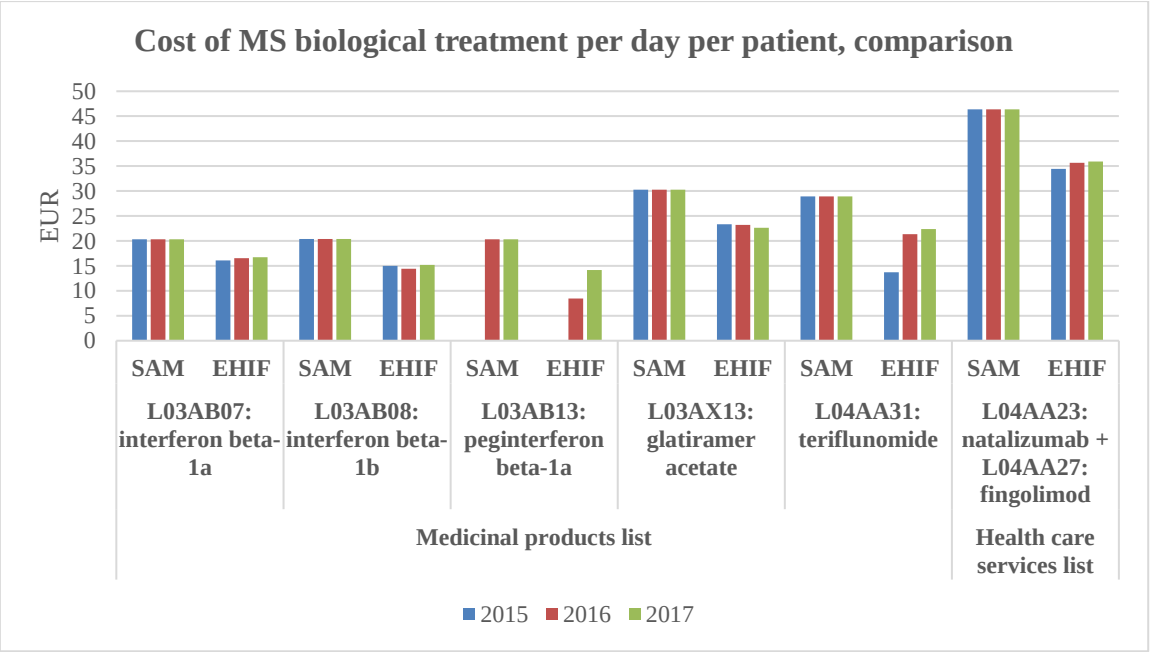

Figure 14. Cost of MS biological treatment per day per patient in 2015–2017 in Estonia, comparison of implicative cost used for the basis of calculations made for SAM data channel and EHIF database.

Comparison of cost of MS biological treatment per day per medication categorized according to reimbursement pathway in 2012–2014 is shown in figure 23 in Appendix 1 and 2015–2017 in represented in figure 24 in Appendix 1.

4.6.1 Small numbers and pulsed therapy

Number of patients using natalizumab and fingolimod based on SAM data channel, EHIF database, SAM database as a source (SAM2 - sold quantities in grams in Estonia, data directly enquired from the State Agency of Medicines data analyst) and hospital databases is represented in figure 15. SAM data channel is referred to as SAM1 and SAM database as SAM2 (SAM as a source, data directly enquired from a SAM specialist). An approach that includes the data about sold quantities in weight units enables a realistic analysis of medications that are used in small amounts.

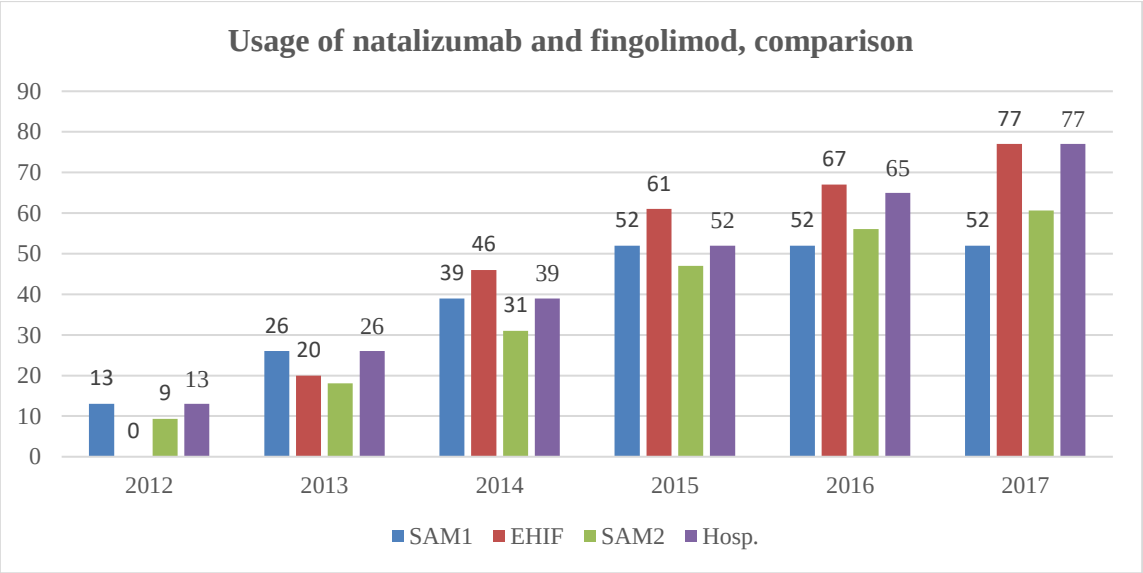

Figure 15. Number of patients receiving natalizumab and fingolimod (conjointly), comparison of databases.

Number of sold vials of alemtuzumab based on EHIF database and SAM database (sold quantities in grams in Estonia, data directly enquired from the State Agency of Medicines data analyst) is represented in figure 16 demonstrate relatively similar data (1 vial equals 12 mg).

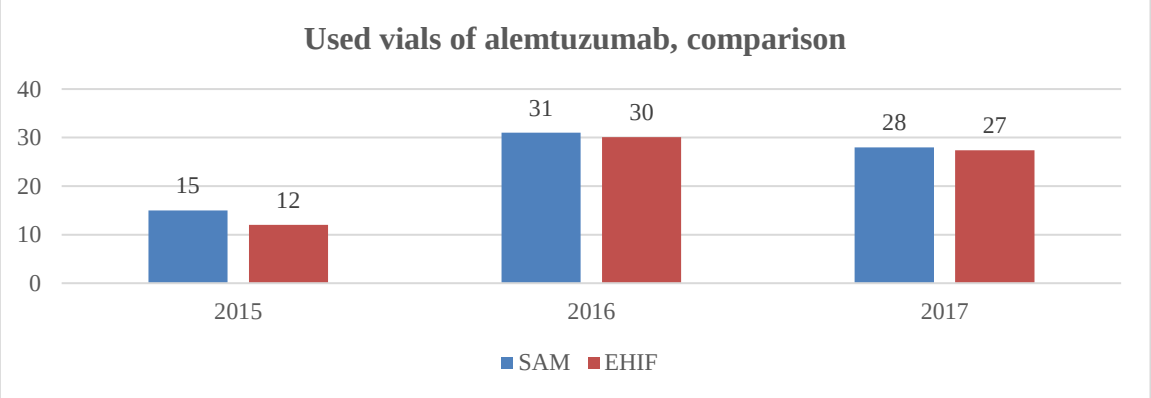

Figure 16. Used vials of alemtuzumab in Estonia, comparison of databases.

4.7 Specialists' perspective and focus-group interviews

4.7.1 Interview with Erki Laidmäe, Head of Division of Medicines and Medical Devices, EHIF

The author of this thesis conducted an interview with Erki Laidmäe, Head of Division of Medicines and Medical Devices, from EHIF and kindly asked to specify how does the EHIF methodologically plan their budget for reimbursing MS biological treatment.

Erki Laidmäe explained that for discount pharmaceuticals (medications reimbursed via list of medicinal products), a general planning methodology is used: EHIF performs time-series analyses and projects the future situation a few years ahead. Specialists of pharmaceuticals evaluate if there have been or will there be any considerable changes.

Analysis of pharmaceuticals that are reimbursed via list of health care services is more complicated. Each year EHIF acquires information from medical societies by sending them letters and asking them to evaluate and assess the need for pharmaceutical treatments allocated to medical services list. It is assessed how should the services should be divided between different medical centres. Also, during EHIF budget planning the information of unmet need is collated with financial means. The specific budget is formed by taking into account the expressed need for treatments by specialists and the EHIF capacity to finance the services. After this is agreed upon, specialists of contract planning calculate the exact charges, taking into consideration both the already existing patients on treatment and patients who will be needing treatment during the next years. The average cost of the "treatment case" (cost per patient) is calculated, contracts with all hospitals providing the services are prepared and contract negotiations begin.

According to Laidmäe, different pathways of reimbursement used in Estonia depend on the amount of need of supervision of a health care provider. Pharmaceuticals in the list of medicinal products can be administered independently and administration of pharmaceuticals in the list of health care services need more supervision by health care specialists.

4.7.2 Interview with Dr. Katrin Gross-Paju, Head of Neurology clinic of West Tallinn Central Hospital

The author of this thesis conducted an interview with Dr. Katrin Gross-Paju, Neurology clinic director of West Tallinn Central Hospital and kindly asked to specify in her opinion, what is the need of MS biological treatment in Estonia, whether or not is the need covered sufficiently, how long should a patient receive biological treatment, what are the circumstances/indications of stopping biological treatment administration and how should the need for biological treatment in MS patients should be evaluated.

"MS is an excellent example why many patients need new and more efficient treatment without delay, immediately when they need them. There are many studies demonstrating convincingly that escalation of treatment, if needed, should be done as soon as possible. Unfortunately delay in escalation will result in significantly worse outcomes for patients. Recent years have demonstrated that whereas we have a large group of patients with benign course there is also a group with active disease course. Recent data confirm that this group can also live a long life without significant disability with timely treatment with next generation biological treatments.

Unfortunately, in Estonia, accessibility to new biological treatment is very poor. The number of patients who can use biological treatments is very small and not increasing. The number of persons who might have had some treatment courses may be increasing but the pre-planned number of patient-cases in this treatment group is not increasing. In comparison, already today, more than 70% of patients on treatments in Sweden receive high efficacy treatments compared to 6.8% in Estonia. One of the reasons is probably inadequate approach to this unmet need by EHIF. According to current reimbursement policy not one hospital can demonstrate the real need for treatment by treating everybody who need treatment, overusing the budget of course, and then getting reimbursement for proven unmet need patient-cases. Consequently, EHIF gets the wrong picture that all hospitals treat more or less the required number of patients."

5 Discussion

5.1 Biological treatment used in patients with multiple sclerosis as a model

Application of new technologies have led to development of highly specific biological treatments with high efficacy. The usage of this specific and expensive treatment is increasing in medicine therefore it is important to analyse the trends of usage and cost of this therapy.

The usage of biological treatment is increasing for many diagnoses. Biological treatments are aiming at more and more precise targets of immune response. All types of biological treatments are available: non-specific (many of them „older generation“ treatments), more modern monoclonal antibodies and oral targeted medications. Indications for all biological treatments are becoming wider. New approaches to treatment and new disease groups will be involved in the near future. Overall trends in the world demonstrate that probably new generation biological treatments will gradually replace older medications.

The problem of biological treatments is not so much the profile of side effects, that are usually mild, but their cost. According to many analyses cost of biological treatments exceeds many times that of the older treatments [2]. Frequently the non-medication costs related to method of administration increase the costs for payers even more [2], [46]. Also, the mode of administration may influence the reimbursement pathway. Medications may be reimbursed either via pharmacy-based reimbursement list (oral targeted, self-administration, acceptable side effect profile) or hospital budget based medical services reimbursement list (intravenous, complicated side-effect profile) [37].

In Estonia, the main payer for medical services is EHIF. EHIF has mainly two different pathways for reimbursement: prescription medication reimbursement (list of medicinal products, pharmacy based) and hospital service based (list of health care services, medical services).

The aim of current thesis was to analyse the use and cost of biological treatments used for MS as a model. MS was selected as a model because it is an excellent example to analyse comprehensively different kinds of biological treatments, older and newer and their reimbursement mechanisms.

MS is a typical autoimmune disease with different types of biological treatments: non-specific (interferons, glatiramer acetate), monoclonal antibodies (natalizumab, alemtuzumab) and oral targeted medications (fingolimod, teriflunomide).

The methods used in the analysis of current thesis involved the analysis of data on „quantities of sold medications“ database (SAM database in Estonia) and EHIF database. EHIF database consists of two different databases: list of medicinal products (pharmacy-based reimbursement) and list of health care services list (medical services reimbursement).

In order to get a comprehensive overview of usage of biological treatments in MS, three different databases were used: SAM (both data channel and SAM as a data source), EHIF and hospital databases (from hospitals that are providing biological treatments for MS).

The hypothesis from the very beginning was that probably the data of only one database will be incomplete. Analysis and combination of data from these different databases should ideally generate a comprehensive overview of usage. Current analysis of accessed data from different databases illustrate the difficulties of getting a reasonable overview of biological treatments even in the setting of one specific disease.

5.2 Problems with SAM database

SAM data channel uses DDDs to refer quantities of sold medications. However, DDD approach does not enable distinction between significantly different interferon beta-1a formulations (medication brands): Avonex and Rebif with different actual daily doses. Also, standard DDD calculations fail to take into account the same medications produced with the same active substance with different dosages (Copaxone).

Therefore, the results of SAM reflecting the number of patients on treatments according to sold DDDs are incorrect for these substances. On the other hand, DDDs and actual mean daily doses coincide for oral targeted (teriflunomide) and non-specific

immunomodulatory (peginterferon, interferon beta 1-b) medications, generally reflecting categorization of only one brand under specific active substance. Small numbers of consumed medications such as fingolimod and natalizumab also provide inaccuracies with only DDD analysis (figures 6 and 17). It is shown on figure 6 that according to SAM data channel, the usage of natalizumab and fingolimod in 2015–2017 was, as calculated from DDDs, 52 patients per each year. Meanwhile EHIF database shows that the respective numbers were 61, 67 and 77. Interestingly, according to hospital databases (figure 15), the respective numbers were 52, 65 and 77. Clearly small numbers create challenges for each database compared, and most probably the most inaccurate results pervade in calculations made with SAM data channel.

5.3 Problems with EHIF database

Natalizumab and fingolimod are reimbursed by the same code (346R) and alemtuzumab is reimbursed by code 349R. Code 346R was added to the health care services list in 2013 and at first, it was only meant for reimbursement of natalizumab. In 2014, the list of health care services was changed in the way that usage of fingolimod was also added under the same code - 346R.

EHIF does not intervene in the choice of a specific drug, consequently they do not have data about usage of natalizumab and fingolimod distinctly. Therefore, it was not possible to analyse separately the usage and cost of these active substances based on EHIF database.

5.4 Comparison of databases

Comparing the usage data between SAM data channel and EHIF databases (Figure 6), the most extreme difference can be seen with the usage of active substance interferon beta-1a (Avonex and Rebif). Calculations made with SAM data channel DDDs show that the number of patients treated with active substance interferon beta-1a in 2015–2017 are 644, 658 and 566 respectively, while EHIF prescriptions database claims that the number of patients who have been prescribed these medications with active substance interferon beta-1a in 2015–2017 is 256, 258 and 224 respectively. Triple difference comes from a statistical error arising significant differences of DDDs from actual daily dosages of different medications categorized under the same active substance.

Glatiramer acetate usage in 2015–2017 according to SAM data channel is 171, 184 and 184 respectively and according to EHIF database 246, 266 and 253 respectively, again demonstrating the influence of the DDD statistical error mentioned earlier.

On the other hand, usage results were also different among active substances which represent only one specific medication. For example, the market newcomer, oral targeted treatment teriflunomide (Aubagio) has been used in 2015–2017 for treating 39, 92 and 145 individual patients respectively according to SAM data channel, but 76, 127 and 183 individual patients respectively according to EHIF database. The differences among two databases in 2015–2017 are about 50%, 30% and 20% respectively for each year. This is not a statistical error but illustrates data collection methods of two different databases. SAM data channel provides statistical numbers of sold medications (reflecting treatment volume) while EHIF prescription database takes into consideration each patient who received at least one prescription a year, no matter how long patients stayed on treatment (not necessarily all 365 days of the year).

5.4.1 Differences of medication usage depending on reimbursement pathway

It is seen from the figures 4 and 5 that pharmaceuticals reimbursed via medicinal products list (pharmacy-based reimbursement) are much more used than pharmaceuticals reimbursed via health care services list (medical services reimbursement). Medications reimbursed via medicinal products list is an open commitment for EHIF and EHIF cannot refuse to compensate the costs of medications that belong to the medicinal products list. In contrast, the number of treatment cases (patients) reimbursed through medical services list is pre-defined between EHIF and the medical centres and cannot be exceeded by hospitals. This is confirmed by EHIF data: pharmaceuticals reimbursed via medicinal products list are significantly more used than pharmaceuticals from hospital services reimbursement list (figure 5). According to SAM data, the amount of „sold medications“ through health medical services list pathway has remained the same – 52 patients through last three years (figure 6). One of the possible explanation for these discrepancies is the difference in the cost of medications. The daily cost of treatment per patient is significantly lower in pharmacy-based reimbursement list compared to medical services reimbursement list (figure 10 and 12).

Figures 3 and 5 demonstrate that the most widely used biological treatments in patients with MS are non-specific immunological medications (historically older and less

expensive) and the least used are monoclonal antibodies (historically newer, but more expensive). Still, there is a trend that the use of non-specific immunological medications (interferon beta-1a and interferon beta-1b) is decreasing while the usage of newer generation therapies is increasing. This is especially true for a market newcomer, an oral targeted prescription medication teriflunomide. The trend is less obvious with medications reimbursed through medical services list but also the use of natalizumab, alemtuzumab and fingolimod is slowly increasing every year.

5.4.2 Mode of administration and reimbursement pathway

There is no clear relation between methods of administration and reimbursement pathway in Estonia. Home-based self-administration medications, such as non-specific immunotherapies (interferons, glatiramer acetate) are reimbursed as pharmacy-based prescription medications. Hospital administrated intravenous monoclonal antibodies are reimbursed via list of medical services through hospital budgets. Oral targeted (both medications are tablets once daily) may be either reimbursed as prescription medications (teriflunomide) or through hospital services (fingolimod). Also, categorization of medications as „older“ or „newer“ is not influencing the reimbursement pathway. A newcomer - teriflunomide (once daily tablet) was immediately reimbursed as prescription medication (pharmacy-based reimbursement).

5.4.3 Cost analysis

For analysing the cost of biological treatment in patients with MS, different calculations were made according to the SAM data channel and EHIF database, including cost of each active substance per year, per month, per day and per patient per day. Please note that cost calculations for alemtuzumab, which is a pulsed therapy, were not included in graphs representing SAM data channel since it is not possible to calculate the costs of pulsed therapy using DDD/1000/inhabitant/day as a unit of measurement. Alemtuzumab requires different approach and the analysis is provided under chapter 5.5.

Figure 7 and Figure 11 illustrate the costs of biological treatments per year of each active substance (except alemtuzumab for SAM data channel) used for patients with MS in 2012–2017. It is seen that the most widely used biological treatment group, non-specific immunological have the lowest cost for one day of treatment but demonstrates the highest

overall cost per year. The overall cost of hospital pharmaceuticals is significantly lower than of prescription medications.

Figure 12 reflects the costs of MS biological treatment per patients per day. The data was categorized only according to reimbursement pathway since EHIF database does not differentiate between fingolimod (oral targeted) and natalizumab (monoclonal antibody). Medications reimbursed via medicinal products list exceed by far the cost of hospital pharmaceuticals.

Since DDD/1000 inhabitants/day is the basis for all calculations based on data from SAM data channel, it is evident that the problems with analysis of cost are similar to problems with analysis of usage: problems with DDDs and actual daily doses also emerge in analysis of cost. Therefore, the most extreme differences in comparing SAM data channel and EHIF database (figure 13) arise from statistical error linked to using DDDs. The most outstanding difference between two databases arising from this statistical error is the cost of interferon beta-1a (per year): 4 199 025.80 EUR in 2017 based on calculations with SAM data channel and 1 367 674.88 EUR based on EHIF prescription database.

Costs per day per patient is much more informative (figure 14, SAM representing an implicative cost per day per patient calculated from reference prices). Our data demonstrate that medications reimbursed via list of health care services exceed significantly the cost of medications reimbursed via list of medicinal products. Still immerse differences exist. The most outstanding difference is between the costs of natalizumab and fingolimod. According to calculations made with reference prices for SAM data channel, cost of both natalizumab and fingolimod per day in 2015–2017 comprised of 46.36 EUR each year and according to EHIF database, cost of natalizumab and fingolimod per day in 2015–2017 comprised of 34.37, 35.67 and 35.89 EUR per each year respectively. However, both data represent that the most expensive treatment per day per patient is treatment that is reimbursed via health care services list.

Comparative calculations of costs per day per medication (figure 23 and 24 in Appendix 1) show that the same statistical error arises as previously. Most dominant difference continually is the cost of active substance interferon beta-1a per day. In 2015–2017 cost of interferon beta-1a per day according to SAM data channel is 13085.86, 13380.10 and 11504.18 EUR respectively while EHIF database shows interferon beta-1a cost per day

4125.42, 4274.44 and 3747.05 EUR respectively. The continuous differences originate from the use of fixed DDD of active substances which do not always reflect the actual daily dose of a substance.

5.5 Small numbers and pulsed therapy

Small numbers (natalizumab and fingolimod) and pulsed therapy (alemtuzumab) need different and/or additional approach for analysis. Figure 15 represents comparison of usage of natalizumab and fingolimod usage according to SAM data channel (SAM1), EHIF, SAM2 database as a source and hospital databases. Calculations with SAM data channel were done as previously using DDDs provided. Calculations with SAM2 database as a source were done with the actual sold quantities in grams enquired from a SAM data analyst. Once again, the data between databases is not compatible.

Alemtuzumab is used in small amounts and according to SAM data channel, in 2016 the usage of alemtuzumab was 0.01 DDD/1000 inhabitants/day. According to raw calculations as done with all the other substances in this thesis, there were 13 patients in 2016 based on SAM data channel receiving alemtuzumab (figures 3 and 4). Since alemtuzumab is administered in different courses and there is no information about whether a patient was currently receiving their first course of treatment (5 vials per year) or second course of treatment (3 vials per year), it is actually not possible to calculate nor analyse the number of patients receiving or the cost of alemtuzumab by using SAM data channel. It is more practical to compare the usage of pulsed therapies according to units of weight or in alemtuzumab's case, used vials. Figure 16 shows that the number of used vials of alemtuzumab based on SAM2 (database as a source) and EHIF database are quite similar, thus this approach could be used in analysing pulsed therapies for the future reference as well.

In this respect clear and comprehensive overview is not attainable. Possibly, the exact numbers of patients on treatments are not vitally important scientifically but the specific worry by neurologists claiming significant unmet need should also need a clear answer: how many and on which treatment MS patients currently are. Also, from the budget planners point of view, EHIF in Estonia, exact data on current expenses for future planning seem to be crucial.

Interviews with EHIF representative and expert neurologist demonstrated how complicated is predicting the need for biological treatments. Also, it seems to be difficult to foresee the future trends of treatment. That was also confirmed by the expert neurologist who explained that best data come from the countries with best current practice of treatment of MS. This brings us back to the importance of precise data from different countries to be able to predict current need and future trends.

5.6 Conclusions

1. The analysis of usage of MS biological treatments is scattered between SAM data channel, SAM2 (as a data source) and EHIF prescription and medical services databases. Non-specific immunological medications (older generation) are currently significantly more used than new monoclonal antibodies.

2. Clear trend indicates quick increase of use of oral targeted prescription medication (teriflunomide, newer generation) and slower increase of use of monoclonal antibodies on expense of decline of non-specific immunological medications.

3. Synthesizing data from SAM data channel, SAM2 and EHIF database does provide general overview of usage and cost of different biological treatments. However, even using all possible databases, the exact number of patients on each biological treatment is unprecise. Even more so, the treatment adherence/persistence per person on biological treatment is complicated.

4. The costs of biological treatments are best characterized by cost per day per patient. The highest cost is seen with new monoclonal antibodies and lowest cost with non-specific immunological treatments. However, the overall costs of non-specific immunological treatments significantly surpass the costs of monoclonal antibodies.

5. Current analysis failed to develop a good prediction model for the adequate use and cost of biological treatments. In the opinion of experts, best clinical practice worldwide should be used for projecting future treatment trends in Estonia.

The following research hypothesis were tested:

- Biological treatments of interest are categorized according to their mechanism (mode) of action (MoA).
    - This hypothesis was not proved. There is no clear or unified categorization of biological treatment.
- Data of usage and cost of biological treatments is scattered and varied in different databases, but provides a broad and comprehensive overview if all the pertinent data is collected
    - Synthesizing data from SAM data channel, SAM2 and EHIF database does provide a general overview of usage and cost of different biological treatments. However, serious methodological problems with DDDs in SAM data channel blur the overall data quality. Also, EHIF database is complete for pharmacy-based reimbursement medications but does not allow to discriminate between two medications reimbursed as medical services. Pulsed therapies with different treatment schedules need very different approach. However, reasonably good overview is feasible.
- Analysis of data of pharmaceuticals that are used in very small amounts is inaccurate in State Agency of Medicines data channel but can be traced through health insurance database
    - SAM2 (special enquiry) and EHIF database provide better data on treatments used in small numbers but discrepancy between patients treated and treatment volume (vials, tablets) poses difficulties.
- The usage and cost of biological treatment of patients with multiple sclerosis has increased in Estonia
    - This is true, mostly with the new generation medications reimbursed.
- The need of biological treatments surpasses the availability for patients with multiple sclerosis
    - According to the medical expert, this is true.
- Analysis of usage and cost of biological treatment is feasible, predicting the actual need is complicated
    - Precise analysis taking into account absolutely all patients on different treatments with well-characterized treatment volume is not feasible. However, from practical and scientific point of view such precision is neither necessary nor feasible (changes in treatments occur every day). According to our analysis some simple changes like normalising SAM

channel reporting – reporting both DDDs and actual treatment dosages and differentiating between different medications would significantly simplify analysis, for instance. Generation of objective overview of use of biological treatments is feasible.

- There are no clear methods proposed to predict future cost of biological treatments.

5.7 Research limitations

A major limitation of this thesis is that according to current data the exact treatment doses/patients/annual costs could not be unambiguously determined. Differences, albeit small and the causes very well recognised were not overcome even by the most sophisticated and comprehensive analysis possible based on these databases.

6 Summary

Biological treatment is an extremely efficient type of treatment performed on patients with diverse diseases. At the same time, biological treatments are very expensive, creating challenges for health care resource allocation management.

This thesis provides a model how to analyse biological treatment in the frame of one certain diagnosis: multiple sclerosis. Collecting various data from different databases was assumed to provide a comprehensive overview of current trends in multiple sclerosis biological treatment. The results show that synthesizing pertinent data is complicated and can often be misleading, but the trends of usage and cost of different MS biological treatment is apparent. In Estonia, medications that are reimbursed via list of medicinal products (the Estonian Health Insurance Fund is obliged to compensate those medications to the limit they are prescribed), are vastly more used than medications reimbursed via list on health care services (usage of these services is limited according to contracts between medical centres and the health insurance). There are also certain limitations of databases influencing the results such as the SAM data channel with demonstrated DDD problems and the EHIF database not differentiating medications coded under the same service code. Discussions with experts shed a light on problems with struggles in covering the need of these effective treatments.

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Appendix 1 - Additional results

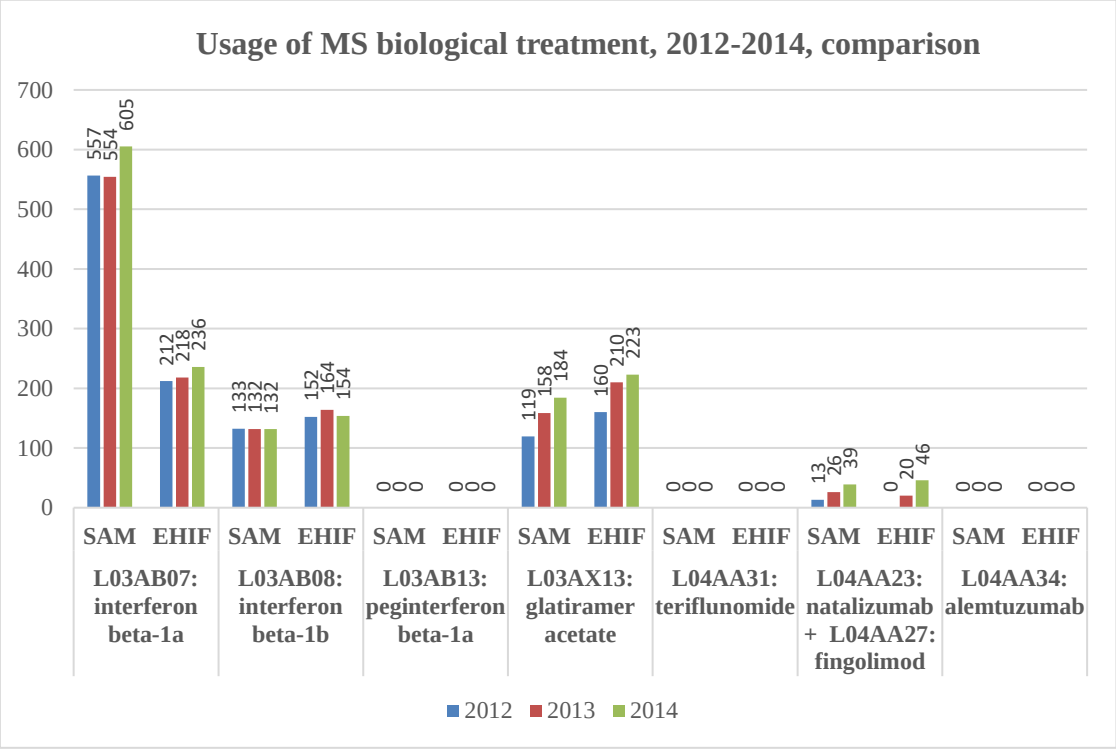

Figure 17. Usage of MS biological treatment per year in 2012–2014 in Estonia, comparison of databases.

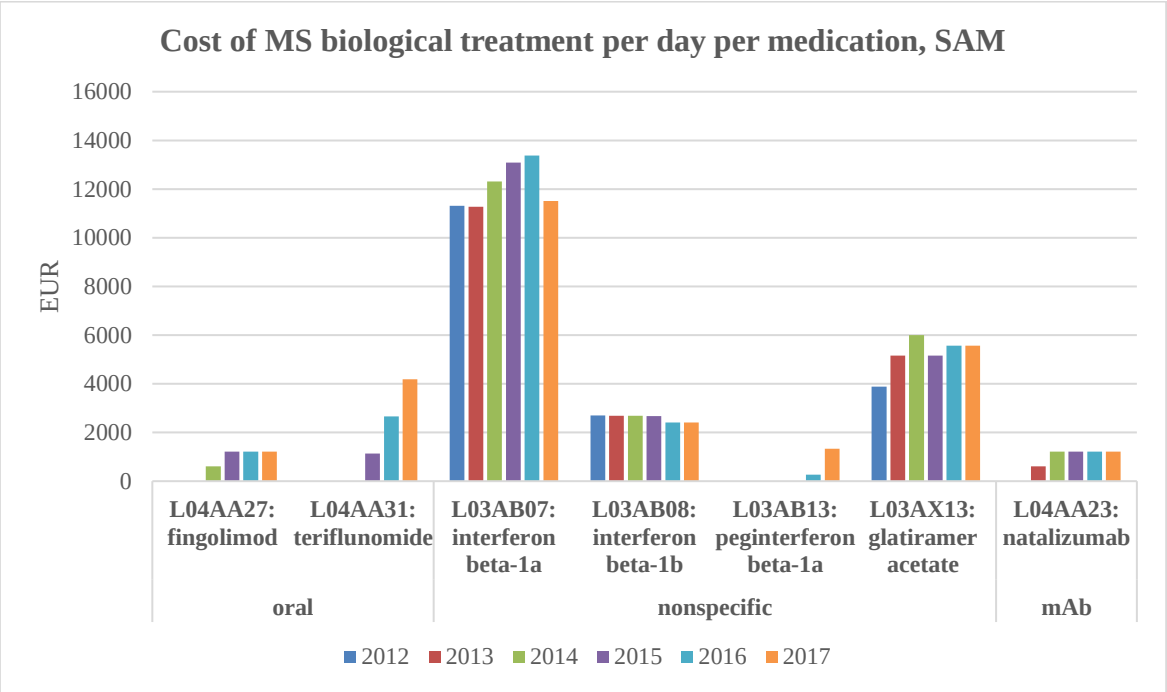

Figure 18. Cost of MS biological treatment per day per medication based on SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

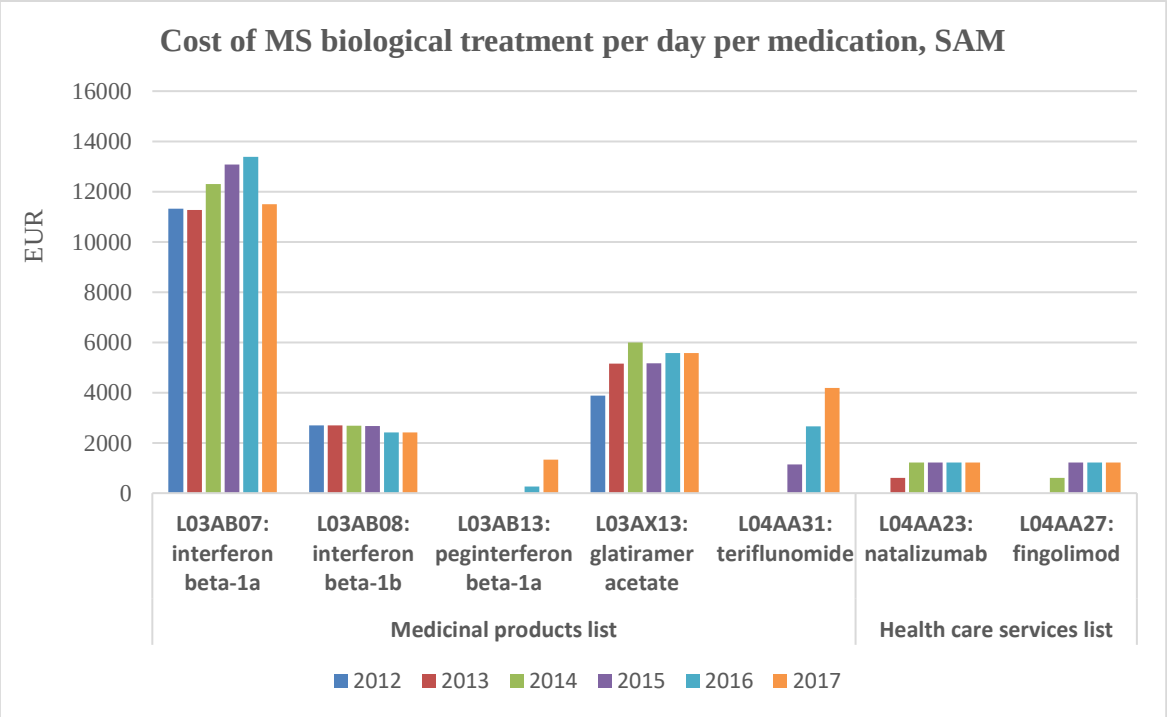

Figure 19. Cost of MS biological treatment per day per medication based on SAM data channel. Please note that the calculations for interferon beta-1a and glatiramer acetate are misleading.

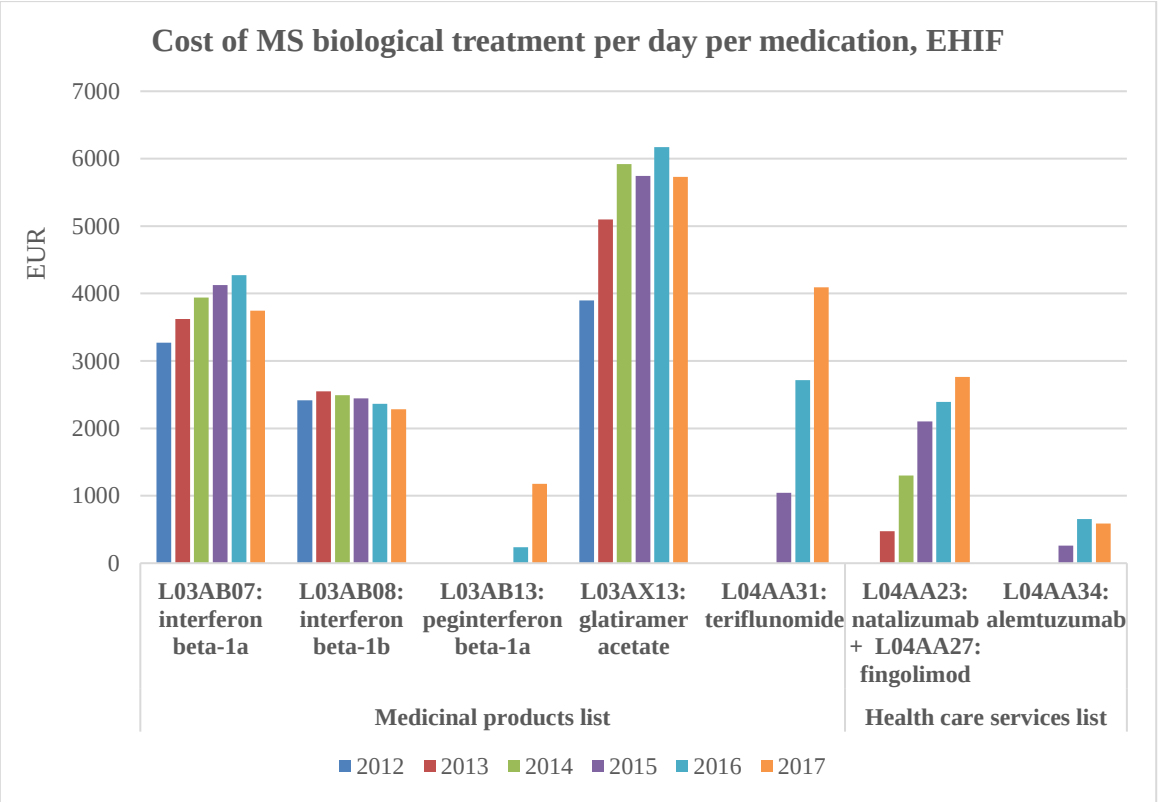

Figure 20. Overall cost of MS biological treatments per day per medication based on EHIF database.

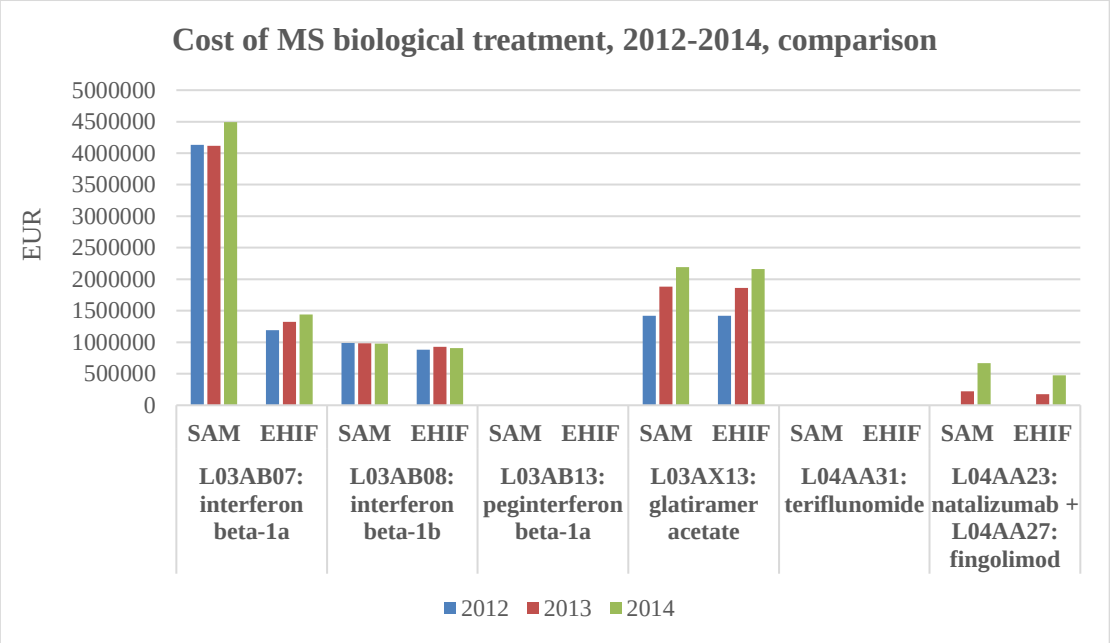

Figure 21. Cost of MS biological treatment per year in 2012–2014 in Estonia, comparison of databases.

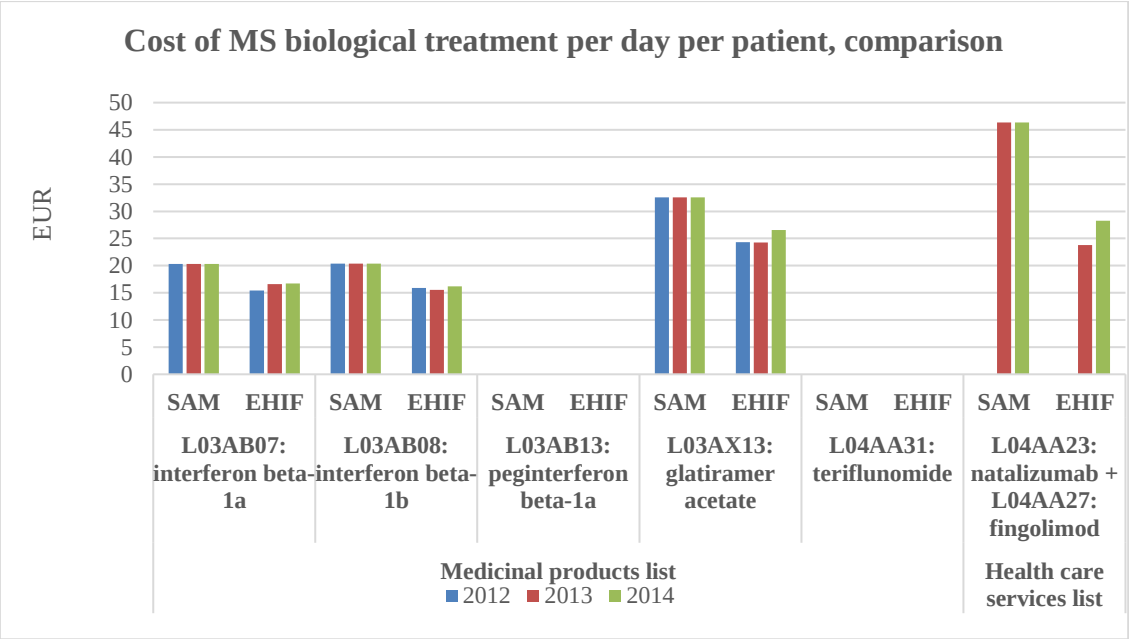

Figure 22. Cost of MS biological treatment per day per patient in 2012–2014 in Estonia, comparison of databases.

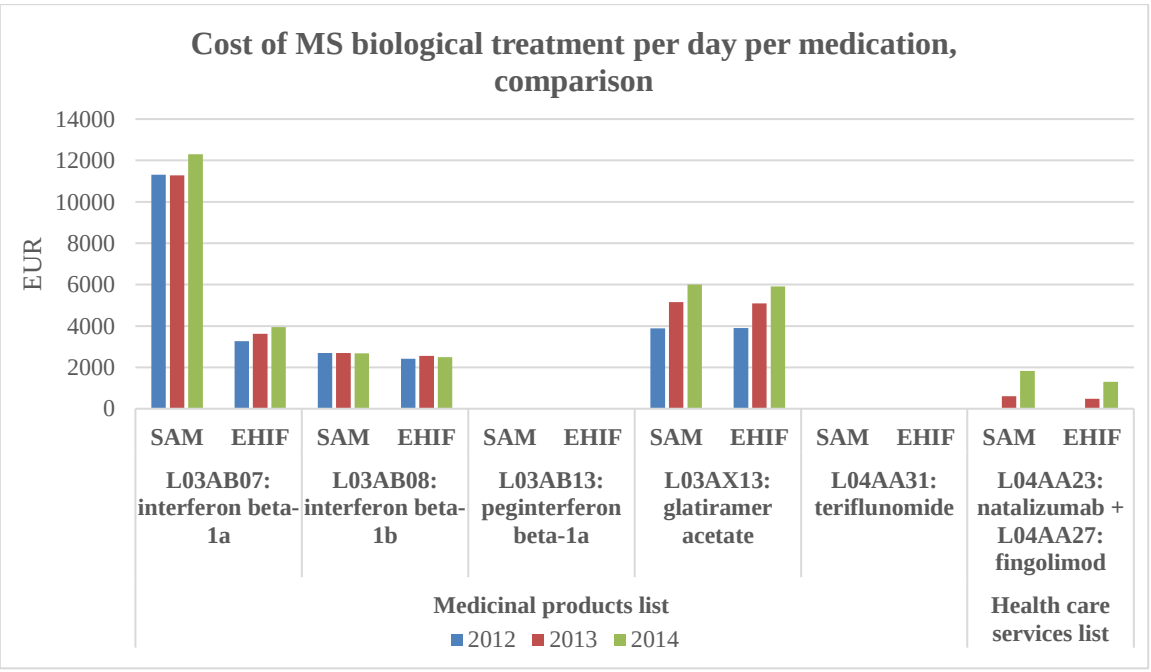

Figure 23. Cost of MS biological treatment per day per medication in 2012–2014 in Estonia, comparison of databases.

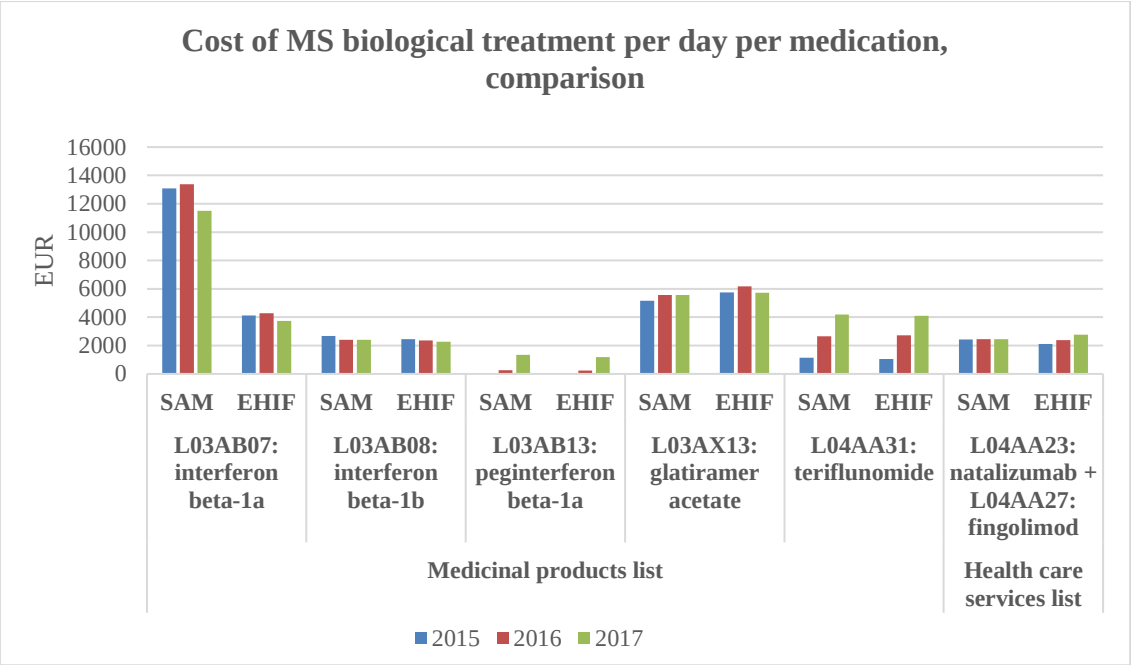

Figure 24. Cost of MS biological treatment per day per medication in 2015–2017 in Estonia, comparison of databases.

Appendix 2 – Biological treatment used for patients with multiple sclerosis in Estonia: mechanisms of actions and indications of medications

L03AB07: Interferon beta-1a, brand name: Avonex, route: intramuscular injection
Indication: „patients diagnosed with relapsing multiple sclerosis (MS); patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis“
Avonex is reimbursed via list of medicinal products.
Interferon beta-1a is produced by using recombinant DNA technology. Avonex applies its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that leads to the expression of several interferon-induced gene products and markers, including MHC Class I, Mx protein, 2',5'-oligoadenylate synthetase, β2-microglobulin, and neopterin. After a single intramuscular dose of Avonex, serum levels of these products remain elevated for at least four days and up to one week. However, it is not definitely clear if its mechanism of actions is mediated analogously as the biological effects illustrated above since the pathophysiology of MS is not fully understood [17].

L03AB07: Interferon beta-1a, brand name: Rebif, route: subcutaneous injection
Indication: „patients diagnosed with relapsing multiple sclerosis“
Rebif is reimbursed via list of medicinal products.
Rebif is produced by using recombinant DNA technology. Rebif has the same amino acid sequence with endogenous human interferon beta. It is produced in mammalian cells (Chinese hamster ovary) and is therefore glycosylated like the natural protein. Interferon beta is produced by different cell types including fibroblasts and macrophages. Binding of interferon beta to its receptors elicits a complex cascade of intracellular events that

leads to the expression of numerous interferon-induced gene products and biological response markers, including 2',5'-oligoadenylate synthetase, β2-microglobulin and neopterin, which may mediate some of the biological activities. The mechanisms by Rebif exerts its actions in multiple sclerosis are not clearly understood [23].

L03AB08: Interferon beta-1b, brand name: Betaferon, route: subcutaneous injection
Indication: „patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years; patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses."
Betaferon is reimbursed via list of medicinal products.
The mechanism of action of interferon beta-1b in patients with multiple sclerosis is not been fully defined. Interferon beta-1b receptor binding induces the expression of interferon-induced proteins like neopterin, MxA protein, IL-10 and ß2- microglobulin which are responsible for the pleiotropic bioactivities of Interferon beta-1b. Immunomodulatory effects of Interferon beta-1b include reduction of pro-inflammatory cytokine production, down-regulation of antigen presentation, the enhancement of suppressor T cell activity, and inhibition of lymphocyte trafficking into the central nervous system [18], [41].

L03AB08: Interferon beta-1b, brand name: Extavia, route: subcutaneous injection
Indication: Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years; patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.
Extavia is reimbursed via list of medicinal products.
Interferon beta-1b wields both immunoregulatory and antiviral activity. The exact mechanism of action of by which interferon-beta-1b exerts its therapeutic effect is still under investigation. Nonetheless, it has been found out that the properties of interferon-beta-1b biological response modification are mediated through its interactions with

specific cell receptors settled on the surface of human cells. When interferon beta-1b binds to these receptors, the expression of several gene products are induced. These products are believed to be the mediators of the biological operations of interferon beta-1b that is able to both decrease the binding affinity and enhance the degradation and internalisation of the interferon-gamma receptor. The suppressor activity of peripheral blood mononuclear cells are also enhanced by interferon beta-1b [19].

L03AB13: Peginterferon beta-1a, brand name: Plegridy, route: subcutaneous injection
Indication: adult patients with relapsing remitting multiple sclerosis.
Plegridy is reimbursed via list of medicinal products.
Plegridy's active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells. Its definite mechanism of action is not fully elucidated since the pathophysiology of MS is not completely understood. It is known that Plegridy binds to the type I interferon receptor on the surface of cells and induces a cascade of intracellular events that lead to the regulation of interferon-responsive gene expression. Plegridy may mediate biological effects such as up-regulation of anti-inflammatory cytokines (IL-4, IL-10, IL-27), inhibition of migration of activated T cells across the blood brain barrier and down-regulation of pro-inflammatory cytokines (IL-2, IL-12, IFN-γ, TNF-α) [22].

L03AX13: Glatiramer acetate, brand name: Copaxone, route: subcutaneous injection
Indication: relapsing forms of multiple sclerosis
Copaxone is reimbursed via list of medicinal products.
The definite mechanism of action of glatiramer acetate is not fully understood. It is assumed to modify immune processes that are believed to be responsible for the pathogenesis of MS: studies propose that glatiramer acetate-specific suppressor T cells are activated and induced in the cell periphery [40].

L04AA31: Teriflunomide, brand name: Aubagio, route: oral
Indication: adult patients with relapsing remitting multiple sclerosis
Aubagia is reimbursed via list of medicinal products.
The specific mechanism of action of teriflunomide is not clear. This immunomodulatory agent inhibits selectively and reversibly the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH) which is needed for the de novo pyrimidine synthesis. It holds

anti-inflammatory properties resulting in reduction of the proliferation of dividing cells that require de novo synthesis of pyrimidine to expand. The therapeutic effect may include reduced number of activated lymphocytes [16].

L04AA23: Natalizumab, brand name: Tysabri, route: intravenous infusion
Indication: single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis for the following patient groups: patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or; patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
Tysabri is reimbursed via list of health care services (hospital medication).
Natalizumab is a recombinant humanized monoclonal antibody against α4-integrin produced in a murine cell line. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Interfering or blocking 4-integrin influences immune cell migration across the blood brain barrier, hence, by blocking the interaction between α4-integrin and vascular endothelial adhesion molecule-1, inhibits transendothelial migration to the central nerve system (CNS). Natalizumab is believed to act to suppress inflammatory activity present at the disease site, and inhibit further exertion of immune cells into inflamed tissues [24].

L04AA27: Fingolimod, brand name: Gilenya, route: oral
Indication: highly active relapsing remitting multiple sclerosis
Gilenya is reimbursed via list of health care services (hospital medication).
Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod acts as a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes. Its therapeutic effect is believed to be prevention of the egression of lymphocytes from lymphoid tissue into the circulation resulting in depletion of lymphocytes. Studies have presented that this reduces the infiltration of pathogenic lymphocytes into the CNS, where they would be involved in nervous tissue damage and nerve inflammation, sparing the CNS from attack by myelin-reactive lymphocytes [20].

L04AA34: Alemtuzumab, brand name: Lemtrada, route: intravenous infusion

Lemtrada is reimbursed via list of health care services (hospital medication).

Indication: adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Alemtuzumab is a pulsed treatment. Initial treatment of two courses:

- First treatment course: 12 mg/day on 5 consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course. Up to two additional treatment courses, as needed, may be considered
- Third or fourth course: 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course in patients with MS disease activity defined by clinical or imaging features

Alemtuzumab, is a recombinant humanised monoclonal antibody that targets glycoprotein CD52 (cell surface molecule expressed on B and T cells), causing lymphocytes depletion. Its exact mechanism of action is not known, however, it may reduce the potential for relapse of tyearõhe disease, delaying disease progression [21].

Appendix 3 – Examples of calculations made for analysing State Agency of Medicines data

Basis for calculations: SAM data channel provides its data in DDD/1000 inhabitants/day

1. costs on the example of interferon beta-1a (prescription medication reimbursed via list of medicinal products) in 2016 was calculated as follows:
interferon beta-1a (L03AB07) DDD/1000 inhabitants/day in 2016 was 0.5
Estonian population in 2016 was 1 315 944 inhabitants
number of daily doses in 2016: 0.5*1 315 944 /1000 = ~658
reference price (per one patient's treatment lasting 28 days, obtained from website www.ravimiinfo.ee for each medication): 569.39 EUR
cost per day per patient: 569.39/28 = 20.34 EUR
cost per day per medication: 20.34*658 = 13 380.10 EUR
cost per year per medication: 13 380.10 *365 = 4 883 734.90 EUR

2.costs on the example of natalizumab and fingolimod (hospital medications reimbursed via list of health care services, code 346R) in 2016 was calculated as follows:
natalizumab (L04AA23) DDD/1000 inhabitants/day in 2016 was 0.02
fingolimod (L04AA27) DDD/1000 inhabitants/day in 2016 was 0.02
Estonian population in 2016 was 1 315 944 inhabitants
number of natalizumab daily doses in 2016: 0.02*1 315 944/1000 = ~26
number of fingolimod daily doses in 2016: 0.02*1 315 944/1000 = ~26
reference price (per one patient's treatment lasting 28 days, obtained from www.riigiteataja.ee, regulation of health care services list for code service 346R) in 2016: 1 298.19 EUR
cost per day per patient of natalizumab: 1 298.19/28 = 46.36 EUR
cost per day per patient of fingolimod: 1 298.19/28 = 46.36 EUR
cost per day per patient code service 346R: (46.36 + 46.36)/2 = 46.36 EUR

cost per day of natalizumab: 46.36*26 = 1220.25 EUR

cost per day of fingolimod: 46.36*26 = 1220.25 EUR

cost per year of natalizumab: 1220.25*365 = 445 390.04 EUR

cost per year of fingolimod: 1220.25*365 = 445 390.04 EUR

cost per year per code service 346R: 445390.04 + 445390.04 = 890 780.08 EUR

3.calculations made based on sold quantities of medications in grams:

according to State Agency of Medicines, the amount of natalizumab sold in 2016 was 105.3 g

one patient's dose of natalizumab pear year is 3.9 g

105.3 g / 3.9 g = 27 patients

Appendix 4 – Examples of calculations made for analysing the Estonian Health Insurance Fund data

1. costs on the example of interferon beta-1a (prescription medication reimbursed via list of medicinal products) in 2016 was calculated as follows:

EHIF prescription database (available from https://www.haigekassa.ee/haigekassa/aruanded-eelarve-ja-statistika/finantsnaitajad/soodusravimite-statistika) shows that the number of patients who have been prescribed this substance in 2016 was 258 patients
and that the cost of prescriptions for active substance interferon beta-1a (including out-of-pocket payments) were 1 560 169.80 EUR
cost per day per patient: 1 560 169.80/258/365 = 16.57 EUR
cost per day per medication: 1 560 169.80/365 = 4274.44 EUR

2. costs on the example of natalizumab and fingolimod (hospital medications reimbursed via list of health care services, code 346R) in 2016 was calculated as follows:

EHIF health care services list database (data enquired via e-mail from an EHIF data analyst) shows that the number of patients who received code service 346R in 2016 was 67 patients
and that the cost of code service 346R in 2016 was 872 383 EUR
cost per day per patient: 872 383/67/365 = 35.67 EUR
cost per day per code service 346R: 872 383/365 = 2390.09 EUR

3. number of alemtuzumab vials used in 2017 according to EHIF
the amount EHIF paid for code service 349R (1 vial of alemtuzumab, 1 vial = 12 mg) was 215 225.9 EUR
reference price for 349R in 2017 was 7 854.96 EUR
215 225.9 / 7 854.96 = ~27 vials

Appendix 5 – ATC-L active substances represented in SAM database

Table 7. Purchased ATC-L pharmaceuticals, DDD. Source: State Agency of Medicine.

ATC-L: Antineoplastic and immunomodulating agents (Group L; DDD/1000 inhabitants/day)

	2012	2013	2014	2015	2016
L: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	8.7	9.36	10.05	10.36	10.73
L02: ENDOCRINE THERAPY	3.85	4.26	4.58	4.61	4.75
L02A: HORMONES AND RELATED AGENTS	0.14	0.18	0.25	0.33	0.44
L02AB: Progestogens	0.01	0.01	0.01	0.01	0.01
L02AB02: Medroxyprogesterone	0.01	0.01	0.01	0.01	0.01
L02AE: Gonadotropin releasing hormone analogues	0.13	0.17	0.24	0.32	0.43
L02AE01: Buserelin	0.01	0.01	0.01	0.01	0.01
L02AE03: Goserelin	0.06	0.08	0.07	0.09	0.1
L02AE04: Triptorelin	0.04	0.08	0.16	0.22	0.32
L02AE05: Histrelin	0.01	0	-	-	-
L02B: HORMONE ANTAGONISTS AND RELATED AGENTS	3.71	4.08	4.33	4.28	4.31
L02BA: Anti-estrogens	0.52	0.59	0.65	0.74	0.77
L02BA01: Tamoxifen	0.46	0.52	0.57	0.63	0.64
L02BA03: Fulvestrant	0.06	0.06	0.08	0.11	0.13
L02BB: Anti-androgens	1.96	2.23	2.33	2.12	2.03
L02BB03: Bicalutamide	1.96	1.99	1.98	1.83	1.69
L02BB04: enzalutamide	-	0.23	0.35	0.29	0.35
L02BG: Aromatase inhibitors	1.23	1.26	1.34	1.38	1.45
L02BG03: Anastrozole	0.49	0.41	0.41	0.41	0.47
L02BG04: Letrozole	0.65	0.77	0.81	0.86	0.85
L02BG06: Exemestane	0.09	0.08	0.12	0.1	0.14
L02BX: Other hormone antagonists and related agents	0.01	0.01	0.01	0.04	0.05
L02BX03: Abiraterone	0.01	0.01	0.01	0.04	0.05
L03: IMMUNOSTIMULANTS	0.89	0.91	1.01	0.97	0.95
L03A: IMMUNOSTIMULANTS	0.89	0.91	1.01	0.97	0.95
L03AA: Colony stimulating factors	0.04	0.05	0.06	0.04	0.05
L03AA02: Filgrastim	0.02	0.03	0.03	0.03	0.03
L03AA10: Lenograstim	0	-	-	-	-
L03AA13: Pegfilgrastim	0.02	0.02	0.03	0.01	0.02
L03AB: Interferons	0.76	0.74	0.81	0.79	0.75
L03AB03: Interferon gamma	-	-	-	-	0
L03AB04: Interferon alfa-2a	0.04	0.03	0.04	0.04	0.03
L03AB07: Interferon beta-1a	0.42	0.42	0.46	0.49	0.5

L03AB08: Interferon beta-1b	0.1	0.1	0.1	0.1	0.09
L03AB10: Peginterferon alfa-2b	0.1	0.09	0.11	0.07	0.04
L03AB11: Peginterferon alfa-2a	0.1	0.09	0.11	0.1	0.08
L03AB13: Peginterferon beta-1a	-	-	-	-	0.01
L03AC: Interleukins	0	0	-	-	-
L03AC01: Aldesleukin	0	0	-	-	-
L03AX: Other immunostimulants	0.09	0.12	0.15	0.13	0.15
L03AX03: BCG bacteria	0	0	0	0	0
L03AX13: Glatiramer acetate	0.09	0.12	0.14	0.13	0.14
L03AX15: Mifamurtide	-	-	0	0	0
L03AX16: Plerixafor	0	0	0	0	0
L04: IMMUNOSUPPRESSANTS	3.96	4.18	4.46	4.77	5.03
L04A: IMMUNOSUPPRESSANTS	3.96	4.18	4.46	4.77	5.03
L04AA: Selective immunosuppressants	0.64	0.65	0.69	0.75	0.83
L04AA04: Rabbit anti-T-lymphocyte immunoglobulin	0	0	0	0	0
L04AA06: Mycophenolic acid	0.22	0.22	0.24	0.24	0.24
L04AA10: Sirolimus	0.02	0.01	0.01	0.01	0.01
L04AA13: Leflunomide	0.39	0.39	0.41	0.42	0.43
L04AA18: Everolimus	0	0	0	0	0
L04AA23: Natalizumab	-	0.01	0.02	0.02	0.02
L04AA24: Abatacept	0	0	0	0	0.01
L04AA26: Belimumab	0	0	0	0	0
L04AA27: Fingolimod	0.01	0.01	0.01	0.02	0.02
L04AA31: Teriflunomide	-	-	-	0.03	0.07
L04AA33: Vedolizumab	-	-	-	0.01	0.01
L04AA34: Alemtuzumab	0	-	-	0	0.01
L04AB: Tumor necrosis factor alpha (TNF-alpha) inhibitors	0.46	0.54	0.62	0.74	0.77
L04AB01: Etanercept	0.12	0.13	0.13	0.14	0.13
L04AB02: Infliximab	0.16	0.2	0.23	0.32	0.37
L04AB04: Adalimumab	0.14	0.15	0.17	0.18	0.17
L04AB05: Certolizumab pegol	0.01	0	0.01	0	0.01
L04AB06: Golimumab	0.04	0.05	0.08	0.09	0.09
L04AC: Interleukin inhibitors	0.04	0.05	0.06	0.05	0.08
L04AC02: Basiliximab	0	0	0	0	0
L04AC03: Anakinra	0	0	0	0	0
L04AC05: Ustekinumab	0.01	0.02	0.03	0.02	0.04
L04AC07: Tocilizumab	0.03	0.03	0.03	0.02	0.02
L04AC10: Secukinumab	-	-	-	0	0.02
L04AD: Calcineurin inhibitors	0.28	0.3	0.35	0.35	0.39
L04AD01: Ciclosporin	0.22	0.23	0.26	0.24	0.25
L04AD02: Tacrolimus	0.06	0.07	0.09	0.11	0.14
L04AX: Other immunosuppressants	2.54	2.64	2.75	2.88	2.96
L04AX01: Azathioprine	0.29	0.27	0.32	0.33	0.32
L04AX02: Thalidomide	0.03	0.02	0.02	0.03	0.02
L04AX03: Methotrexate	2.2	2.31	2.37	2.48	2.57
L04AX04: Lenalidomide	0.03	0.04	0.04	0.04	0.04

L04AX05: Pirfenidone	-	0	0	-		0.01
L04AX06: Pomalidomide	-	-	-		0	0