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Intravenous or subcutaneous rituximab for maintenance therapy of mantle cell lymphoma
a budget impact analysis

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INTRAVENOUS OR SUBCUTANEOUS RITUXIMAB FOR MAINTENANCE THERAPY OF MANTLE CELL LYMPHOMA: A BUDGET IMPACT ANALYSIS

Mémoire présenté pour l'obtention

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Intravenous or subcutaneous rituximab for maintenance therapy of mantle cell lymphoma: a budget impact analysis

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Abstract

Background

Mantle cell lymphoma is a cancer of the lymphocytes. Maintenance therapy can be performed with rituximab, administered intravenously or subcutaneously. Both formulations have different administration-associated costs and drug costs. The IV cost is influenced by dose, influenced by the body surface of the patient, whereas SC rituximab is at a fixed-dose.

Aim

The primary objective was to compare the global cost of IV (depending on the body surface area) versus SC rituximab to identify the most favorable formulation in a cost-minimization way, in routine medical practice. Discounts that could be proposed were considered.
A second objective was to focus on the time spent by patients in the hospital for each formulation.

Methods

A retrospective observational study comparing IV and SC rituximab was performed on 13 mantle cell lymphoma patients treated between 2015 and 2020 (representing 48 IV and 50 SC administrations). Several times and costs associated with rituximab administration were collected. An economic model was used.

Analysis

Administration times were 90 min and 5 min (+15 min observation time) for IV and SC rituximab. Nurses' involvement was longer with SC rituximab (16,50 min vs 13,65 min). Drug preparation times by pharmacist were 294 seconds and 0 for IV and SC rituximab. Materials costs were 16,86 € and 5,01€ for IV and SC rituximab.
Rituximab cost for 1 cycle of maintenance therapy varied from 1 191,48€ to 1 787,22€ for IV rituximab. The fixed cost of SC rituximab was 1 398,67€. Additional non-drug costs with IV rituximab (1 injection) were 13,40 € (representing around 1% of the drug cost).
With a 10% IV discount, SC rituximab was cost saving for patients > 1.86 m^2. From 20% IV discount, IV rituximab was cost saving for patients ≤ 2,13 m^2.
If there were 15% SC discount and up to 20% IV discount, SC rituximab was cost saving for patients >1.86 m^2. From 15% and 30% SC and IV discounts, IV rituximab was cost saving for patients ≤2.13m^2.

Mean time spent in the hospital were 3h15 (3h15±0h38) and 2h12 (2h12±1h13) for IV and SC administrations.

Conclusion
IV rituximab was found cost saving in routine medical practice in most situations. SC formulation was cost saving in only three situations: 1) with no discounts, 2) with only 10% IV discount and 3) when there was 15% SC discount and 20% or less discount on the IV form.
Patient time in the hospital was approximately 1 hour longer with IV rituximab.

Keywords: mantle cell lymphoma, maintenance therapy, rituximab, administration route, budget impact analysis.

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List of abbreviations

ASCT = Autologous stem cell transplantation
BIA = Budget impact analysis
BSA = Body surface area
CLL = Chronic lymphocytic leukemia
CTSQ = Cancer treatment satisfaction questionnaire
DLBCL = Diffuse large B-cell lymphoma
DPA = Drug preparation area
EMA = European Medicines Agency
FDA = Food and Drug Administration
FL = Follicular lymphoma
HCP = Health care professional
HL = Hodgkin lymphoma
HRQoL = Health-related quality of life
IV = Intravenous
LDH = Lactate dehydrogenase
mAb = Monoclonal antibody
MCL = Mantle cell lymphoma
MIPI = Mantle cell lymphoma international prognosis index
NHL = Non-Hodgkin lymphoma
RASQ = Rituximab administration satisfaction questionnaire
SC = Subcutaneous
SD = Standard deviation
SmPC = Summary of products characteristics
VAT = Value-added ta

1. Introduction

1.1. General introduction

Mantle cell lymphoma (MCL) is an aggressive, generally incurable, cancer of white blood cells. MCL is a B-cell non-Hodgkin lymphoma (NHL) [1–3].
The diagnosis is based on several techniques. The treatment depends on the age and the clinical status of the patient. However, in almost all cases, the last stage of the therapy consists of a maintenance phase with rituximab, which prolongs the remission duration and the overall survival [2,4].
Almost all forms of B-cell NHL are treated with rituximab, a monoclonal antibody that targets CD20, a transmembrane protein present on most malignant B-cells. For years, intravenous (IV) rituximab has been standard care of maintenance therapy for MCL. However, for different reasons, subcutaneous (SC) rituximab has been developed. This formulation has many advantages. For 20 years, the pharmaceutical company Roche has almost had exclusivity concerning the sale of IV rituximab. This exclusivity can be obtained thanks to a patent, which is a document that can be filled in, to protect an invention or a discovery and especially the resulting investments [5].
Given that drug discovery and development is a very expensive and long process, pharmaceutical companies developing such drugs as rituximab want to obtain a patent in order to protect their invention and to get exclusivity on the market in a specific disease.
Once a patent expires, anyone can have access to the drug composition and to the process allowing them to produce a biosimilar at much lower costs. And that is what happened with rituximab. For years, Roche had the exclusivity thanks to their patent but once this patent expired, other companies made biosimilars at much lower costs, forcing Roche to lower the cost of their IV formulation. Therefore, Roche decided to develop a SC form of rituximab in order to get a patent for this formulation and to regain the exclusivity. But this new SC formulation is more expensive than the IV biosimilars.

With this in mind, IV biosimilars could appear much more interesting economically speaking but there are other criteria to consider. For example, an IV injection takes 1h30 while a SC injection is only 5 minutes (plus 15 minutes of observation time), also, pharmacists are much more solicited for IV drug preparation, …
The aim of this economic study is to evaluate which form is the most interesting, economically speaking. Not only taking into account the price of the drugs but also other criteria related to time and cost savings, such as the duration of hospital stays, the time spent by the nurses, the preparation time needed by pharmacists, the cost of the materials, ….

1.2. Mantle cell lymphoma

MCL is an aggressive, generally incurable B-cell lymphoma which is a cancer of lymphocytes. This lymphoma originates from the external zone of lymph nodes, called the “mantle zone”. That is there that MCL takes his name. MCL is classified as a peripheral B-cell lymphoma. The lymphoma originates from peripheral B-cells from the inner mantle-zone of secondary follicles[6].
Lymphomas are divided into two types: Hodgkin lymphoma (HL), characterized by the presence of Reed-Sternberg cells, a specific type of cells, and non-Hodgkin lymphoma (NHL). MCL is a subtype of NHL, which can be formed from T-cells or B-cells, such as MCL. Patients are very often affected by MCL with stage III or IV, for the reason that NHL aren’t often

diagnosed until reaching an advanced stage, in contrast to HL which are used to be diagnosed at an earlier stage [7].
This lymphoma is characterized by the involvement of lymph nodes, spleen, blood, and bone marrow. Those are also involved in other lymphomas. However, in the MCL, the blood, the spleen, and the bone marrow are more involved than in other lymphomas. It is not explained; a hypothesis is that this particular lymphoma finds in these places a more favorable environment to develop [1–3,8–11].

1.2.1. Epidemiology and global burden of MCL

Patients affected by this lymphoma have a median age of 60 to 70 years. In 2009, the median survival was three to four years. Men are two to three times more affected than women. Nowadays, median survival is around five years[1–3,8–11].
NHL represent 80% of all lymphoma, the remaining 20% is HL. In Europe, 5-9% of lymphomas are MCL. In the US, MCL represent 5% of all lymphomas [8,12].
MCL is a rare lymphoma. In the UK, the annual incidence is one case per 200 000 people [8,9].
In 2017, approximately 2 000 patients were affected by a NHL in Belgium. As previously said, older people are more affected by MCL. NHL is the 8th most common cancer in Belgium. Between 2015 and 2020, 13 constitutive patients were treated from MCL at the hospital CHU-UCL Namur, Yvoir. That represents a very small number of patients [10].

The cost of the treatment is high, explained by the length of treatment, the costs of the research and development, and also by the small number of patients affected. It is very difficult to estimate the INAMI budget dedicated to this cancer. But what can be stated is that the cost of the drug represents a major part of this budget.
Drug cost depends on the dose. For an SC administration, the dose is always 1400 mg, whatever the body surface area (BSA) of the patient. But, for an IV administration, the dose is 375mg/m^2, meaning that the dose depends on the BSA of the patient. The ex-factory cost of a vial of 1400mg (for SC rituximab) is 1398,67€. One vial of 100 mg of IV rituximab is 198,58€ and, depending on the BSA of the patient, usually, 6 to 9 IV vials are needed for one administration. Thus, the ex-factory price of one IV administration ranges from 1 191,48€ to 1 787,22 €.

1.2.2. Pathobiology and pathogenesis of MCL

A chromosomic translocation between chromosomes 11 and 14 (t (11;14) (q13; q32)) is the putative oncogenic event of MCL (see in figure 1). This translocation leads to a deregulation of the gene CCDN1 and thus overexpression of cyclin D1, a protein encoded by this gene, which plays a role in the regulation of the cell cycle. Cyclin D1 overexpression is presented at mRNA but also at protein levels and leads to a deregulation of the cell cycle, progressively leading to lymphoma 12,13.

This resulting overexpression is not the only oncogenic event leading to MCL. Other genetic alterations called secondary genetic alterations appear and explain the aggressivity of MCL. In 40 to 75% of MCL patients, a mutation causing the inactivation of the *ATM* and/or the *CHK2* genes is observed. That leads to a deregulation of the DNA damage response pathway, resulting in increasing genomic instability. This instability promotes the translocation between chromosomes 11 and 14. That explains also why MCL is one of the neoplasms with the highest genomic instability. That instability doesn't only promote the specific translocation between chromosomes 11 and 14 but promotes also additional oncogenic events. These additional oncogenic events are needed for the expansion of MCL cells and affect for example the pathway of p53, a tumor protein, inactivated in more than 50% of cancers [11,14].

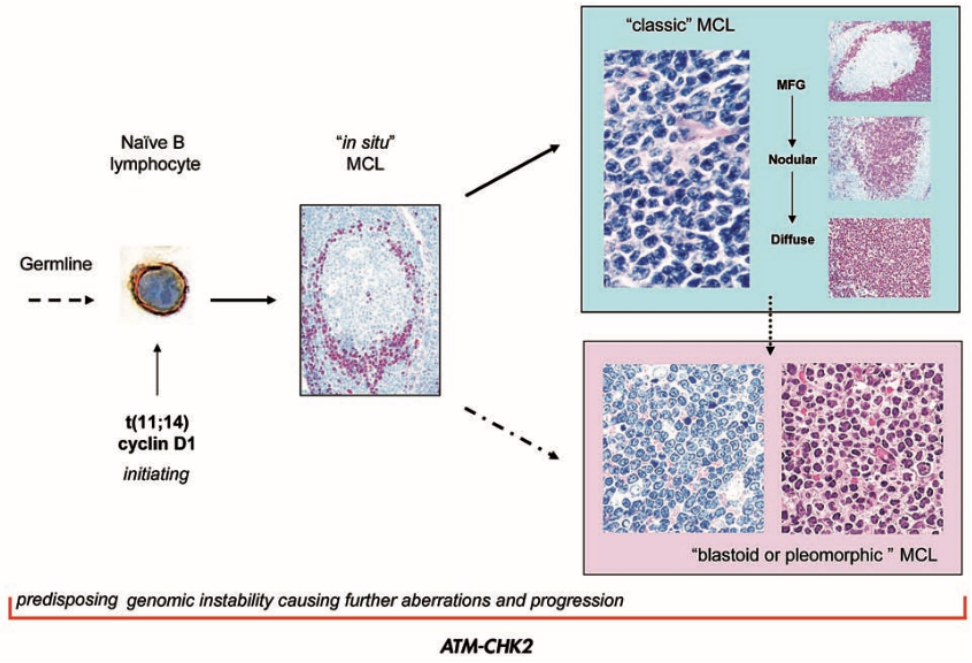

Figure 1: Pathogenesis and morphological representation of MCL. Cyclin D1 is immunostained in red by the alkaline phosphatase anti-alkaline phosphatase complexes technique. CD20 is stained on the naïve B-cell, by immunoperoxidase. Giemsa coloration is used to stain in blue classic and blastoid MCL. Pleomorphic MCL is stained in red by hematoxylin and eosin [11].

1.2.2.1. Clinical presentation and diagnosis

MCL affects lymph nodes but also extranodal sites as the peripheral blood, bone marrow, and gastrointestinal tract. According to the stage of the tumor, the morphology is different. In the beginning the tumor substitutes the mantle zone. Then, the tumor invades germinal centers in lymph nodes, which constitutes a nodular pattern. And, ultimately, nodules fuse together. A PET-CT scan is generally performed to evaluate the disease extension at baseline [11,14].

The diagnosis is based on several techniques. First, a biopsy of enlarged lymph nodes enables the visualization of infiltrates of monomorphic small to medium-sized cells with a particular histological pattern: nodules with irregular contours, which are present in most of the cases. However, some cases are different morphologically speaking, not forming nodules. These other histological patterns could be blastoid, pleomorphic, or small cells (see in figure 1). It is furthermore important to remain vigilant with regard to the diagnosis [11,14].

After the biopsy, immunophenotyping provides information on antigens presented on the cells surface. The antigen CD20, for example, is strongly expressed on cancer cells in MCL while CD20 is less expressed in the case of chronic lymphocytic leukemia (CLL). Immunophenotyping can be a very useful diagnostic tool. However, like other tools, the results have to be interpreted with caution since abnormal phenotyping can be presented. For this reason, immunohistochemistry is very useful to confirm the diagnosis. This method can detect proteins like cyclin D1, which is overexpressed in MCL and not in other lymphomas that could have been confused so far. This test is positive 95% of the time. In addition, fluorescent in situ hybridization enables visualization of the translocation [11,14].

1.3. Treatment

The treatment differs according to the age and the health status of the patient. Nevertheless, in almost all B-cells NHL, rituximab is considered as standard care. Rituximab is given during the

induction phase of the treatment and had also proven efficacy during the maintenance phase of the treatment, even if some mechanisms are still unclear [5].
For young and fit patients, able to support aggressive therapy, the treatment consists of a combination of chemoimmunotherapy, containing rituximab, called R-CHOP or R-DHAP. This first phase of the treatment is then followed by consolidation with autologous stem cell transplantation (ASCT) and then a phase of maintenance with rituximab. For older and frailer patients, the standard therapy of MCL also consists of chemotherapy combined with rituximab (R-CHOP), followed by rituximab maintenance [2,4].

1.3.1. Rituximab

Rituximab is a human/murine anti-CD20 monoclonal antibody which has proven its efficacy and safety in the treatment of MCL. Rituximab was the first monoclonal antibody (mAb) approved for cancer treatment. As introduced previously, this antibody is usually used during 2 phases of the treatment: in the initial phase in combination with chemotherapy and also in the maintenance phase [15,16].

1.3.1.1. Research and development history of rituximab

Rituximab was the first mAb approved for cancer treatment. It was approved for use in relapsed indolent NHL in 1997 by the Food and Drug Administration (FDA), in the United States. In Europe, it was approved in 1998 by the European Medicines Agency (EMA). In 20 years, its sales reached approximately $93,74 billions [5,15,17].

1.3.1.2. Mechanism of action

Rituximab is a mAb that has a high affinity for a transmembrane protein presented on most malignant B-cells: CD20. This antigen is not expressed until the maturation of the cell. What is very interesting is that this transmembrane protein is only expressed on malignant cells which makes it the “perfect” anti-cancer target. The biological function of CD20 isn’t completely clear. It would be involved in calcium storage in B cells. Several mechanisms lead to the elimination of the CD20+ cells after rituximab binding but the details of these mechanisms are not the topic of this project [5,15].

1.3.1.3. Proven efficacy of rituximab in MCL

Rituximab has proven efficacy during the induction phase of the treatment and also during maintenance therapy.

Concerning induction therapy, it has proven efficacy in older patients with MCL. The paper by Griffiths R. et al. concluded that “first-line chemotherapy including rituximab is associated with significantly improved survival in older patients diagnosed with MCL” [18].

Concerning maintenance therapy, the paper by Kluin-Nelemans H.C. et al. confirmed the proven efficacy of rituximab. Maintenance therapy with rituximab “reduced the risk of progression or death by 45%” in comparison with interferon-alpha”. At 4 years, 58% of the patients who received rituximab were still in remission versus 29% of those who received interferon alfa”. But the paper noticed that “the influence of maintenance therapy with rituximab on the duration of remission was detected in patients who received R-CHOP but not in those who received R-FC”, as induction therapy. Concerning overall survival, the paper said “there was a significant modification of the effect of maintenance therapy according to the induction regimen with a survival gain at 4 years among the patients who received R-CHOP

(87% in the rituximab group vs. 63% in the interferon alfa group) but not among the patients who received R-FC" [4].

Thus, rituximab in maintenance therapy doesn't only prolong the progression-free survival but prolongs also the overall survival, in patients previously treated by R-CHOP. This wasn't only the case for older patients as patients involved in the study by Kluin-Nelemans et al. but that was also the conclusion of the paper by Le Gouill S. et al, which concerned younger patients, eligible for ASCT. This paper compared two groups: one received rituximab in maintenance therapy and the other was an observation group. It is said "the rate of progression-free survival at 4 years was 83% in the rituximab group versus 64% in the observation group (P<0.001). The rate of overall survival was 89% in the rituximab group versus 80% in the observation group (P=0.04)". Rituximab in maintenance therapy increases the progression-free survival and the overall survival of patients [3,4].

1.3.2. Rituximab maintenance

Actually, there are two "cards to play" in order to improve a poor prognosis. Either it is possible to search for a better induction treatment to improve the duration of response, or it is possible to engage maintenance therapy which is a postinduction strategy.
In MCL, first-line treatment is often effective but, unfortunately, relapse or progression occurs frequently (usually within two to three years). Partial remissions, relapses, or progressions are the reason why maintenance therapy can be engaged. The aim is to prolong the duration of remission and also the overall survival of patients, what was proven above [4].

1.3.2.1. Treatment regimen

The maintenance phase with rituximab lasts a minimum of two years (if no arrest or interruption is requested for medical reasons). The treatment regimen is described in the summary of product characteristics (SmPC). It is a kind of package leaflet for a medicine describing how to take it and at what dose. It is indicated that maintenance therapy is constituted by 12 injections. Patients generally receive the 12 injections at a frequency of one injection every 2 or 3 months, for 2 or 3 years, depending on their age and their health status.
For a SC administration, the dose is 1400 mg and is fixed. For an IV administration, the dose is 375 mg/m^2, calculated on the basis of the BSA of the patient, indicated in square meter.
That represents a huge cost, as already introduced above [3,4,14].

1.3.2.2. Among younger patients

Originally, ASCT was considered such as consolidation therapy after chemoimmunotherapy. But for some patients, ASCT isn't possible. For this reason, rituximab as maintenance therapy has been explored. As already said (see section 1.3.1.3. Proven efficacy of rituximab), a study by Le Gouill et al. concluded that **"**rituximab maintenance therapy after transplantation prolonged event-free survival, progression-free survival, and overall survival among patients with mantle-cell lymphoma who were younger than 66 years of age at diagnosis". This study was included in the meta-analysis of Hilal et al. confirming the benefit of maintenance therapy with rituximab after ASCT consolidation [3,13].

1.3.2.3. Among older patients

Older patients are often considered ASCT-ineligible patients. For them, only rituximab can be proposed as maintenance therapy. As already said (see section 1.3.1.3. Proven efficacy of rituximab), a study of Kluin-Nelemans et al., addressing older patients, showed that "maintenance therapy with rituximab almost doubled the duration of remission in patients who had a response to induction therapy and significantly improved overall survival among patients

who had a response to R-CHOP". Interestingly, the study results showed that rituximab maintenance therapy presented not only an advantage concerning progression-free survival but improved also overall survival of patients who had previously been successfully treated by R-CHOP [4].

Unfortunately, this study is the only one exploring the question of the efficiency of rituximab maintenance for ASCT-ineligible patients. That is why, nowadays, a clinical trial (NCT01865110) is still ongoing with the aim of investigating the efficacy of rituximab maintenance therapy for patients who are ASCT-ineligible, as older patients for example [4,13].

1.3.3. IV administration challenges

In the beginning, rituximab was administered only by IV injection, but this administration route represents some issues. While SC administration could have many advantages.

As mentioned in a paper by Shpilberg et al., IV administrations present some difficulties including "the need for trained personnel, dedicated infusion facilities, dose calculation, aseptic preparation of required infusion volumes, and extended post-infusion observation; long infusion times and slow workflow for medical staff; potential difficulties with IV catheter placements; risk of infusion-related reactions and complications leading to hospitalization and additional costs; costs associated with the placement of permanent IV lines" [16]. A large number of challenges linked to the IV form could be countered by SC administration. It could shorten the administration time and decrease the burden links to the infusion. It could also be useful in situations where IV administration is too complex because of poor local conditions. For the reason that SC injection is administered at a fixed-dose, it could also enable to decrease dose calculation errors, to avoid wastage, and to decrease preparation time. SC administration could simply facilitate rituximab administration and reduce health-care costs linked to IV administration but an issue related to SC administration could be the limitation of drug volume [15,16,19].

All those advantages in favor of the SC formulation explain why, in general, healthcare providers but also patients, prefer SC injection. Preferences are discussed further (see section 1.4.4. Patient preferences) [19].

1.3.4. Approval of SC administration

SC administration of rituximab was approved based on the results of the SABRINA study, a randomized, open-label, phase 3 trial, performed in 113 centers in 30 countries, which concluded that "intravenous and subcutaneous rituximab had similar efficacy and safety profiles, and no new safety concerns were noted. Subcutaneous administration didn't compromise the anti-lymphoma activity of rituximab when given with chemotherapy". It has been proven that the clinical activity and the safety were equivalent in both forms. Adverse events were also similar in both groups. It was also the same with adverse events of grade 3 or higher and serious adverse events. Only administration-related side effects were more common in the SC group but were mainly grade 1 or 2 injection-site reactions (erythema, pruritus, and pain) [15,20,21].

This biosimilarity between both formulations was proven for follicular lymphoma (FL), another NHL, but not specifically for MCL. That is explained by the fact that FL was concerned by maintenance therapy before MCL. However, in medical routine, the results are extrapolated to MCL via a concept called indication extrapolation [15,20,21].

1.3.4.1. Indication extrapolation

In fact, if such studies as SABRINA should be performed for each specific subtype of NHL, it would be very expensive for pharmaceutical companies developing such biosimilars as IV rituximab. Moreover, that would inevitably discourage the development of biosimilars and it would reduce the stimulation of market competition.

Rituximab has several indications and can be used in different pathologies, given the fact that some pathological mechanisms are the same in multiple diseases. For that reason, conducting a safety and efficacy study for each indication of a drug would be impractical and cost-prohibitive. As said in EMA Guideline about similar biological medicinal products containing mAb, "extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the results of the overall evidence provided from the comparability exercise and with adequate justification" [15,20–23]

1.4. Intravenous versus subcutaneous rituximab

The next section presents the differences related to time and to cost, between IV and SC rituximab.

1.4.1. Differences related to time

SC rituximab presents two main advantages in terms of time savings, which are a reduced active healthcare professional (HCP) time and a decreased chair time [21,24].

1.4.1.1. Active healthcare professional time

The definition of active HCP is formulated in a paper by De Cock et al.as the "time actively dedicated by any staff member on pre-specified tasks". This study concluded on a statistically significant decreased active HCP time in the treatment room and in the drug preparation area (DPA)[21,24].

1.4.1.1.1. Drug preparation time and pharmacists' time

The preparation by pharmacists of an injection of SC rituximab is shorter than the preparation of an IV injection. One of the reasons explaining the reduction of preparation time needed for a SC injection stands in the dose. For an IV administration, the dose depends on the BSA of the patient. Thus, the dose has to be calculated, whereas, for a SC administration, the dose is fixed. Consequently, the preparation time needed by pharmacists is reduced. In the microcosting study by Mihajlovic et. al., it was found out that means preparation times were 242,57 and 226,5 seconds for an IV and SC administration respectively. In the SMABcare study, preparation times were 546 and 210 seconds for IV and SC rituximab [25–27].
In the pharmaceutical unit, only drug preparation time differs according to the administration way. "The preliminary steps of supply and storage of pharmaceuticals products at pharmacy were similar for both formulations", as said in the paper by Fargier et al. [27].

1.4.1.1.2. Administration time and nurses' time

Nurses are responsible for the administration of rituximab. The duration of the administration is different depending on whether it is IV or SC rituximab that is administered. In the SmPC, recommended administration times are 1h30 and 20 min (5 min of injection plus 15 min of observation) for IV and SC rituximab. For the IV injection, there is no observation time after the administration whereas, for the SC rituximab, there is 5 min of injection and 15 min of observation time after the injection.

Regarded these administration times, it could seem logical that nurses will save a lot of time with SC administration since an IV administration lasts approximately 1h30 whereas a SC administration lasts only 20 minutes, taking into account the observation time. However, if a decrease of nurses' time was observed in some studies by using SC rituximab, in other studies, that wasn't the case.

The SMABcare study raised the fact that "time-saving for nurses was not significantly different as expected, because, in IV administration, a nurse can take care of several patients at a time and need not necessarily be physically present with a given patient throughout, in contrast to SC administration". The nurses' times were estimated to 23,7 and 11,8 min for IV and SC administrations. The paper by de Cock et al. reported ranges of nurse time: 12,2 min to 40 min and 7,8 min to 19,9 min for IV and SC rituximab respectively. In the microcosting study by Mihajlovic et. al., the mean nurses' times observed were 13,65 and 16,50 minutes for IV and SC administration respectively. That was the only study reporting a nurses' time longer with the SC formulation [24,26–29].

Based on 4 studies the paper by Franken et al. cites "a reduction between 32 and 47% for time of healthcare professionals". Those percentages have to be taken carefully because, in some studies, not only monotherapy with rituximab but also combination therapy was taken into account, which influenced the results. Surprisingly, the study of Mihajlovic J. et al. was the only one observing a 15% increase in the time of HCP, explained as follows: "An SC injection requires active nurse time during the entire administration time, whereas an IV infusion only requires time for connecting and switching infusion bags and checking the infusion pump". Moreover, as justified in the paper by Mihajlovic et al., SC administration is a new method, and nurses are not yet trained and accustomed as they are for IV injections [25,30].

In short, HCP time is reduced with SC rituximab, concerning drug preparation. On the contrary, active nurses' time during administration seems likely to increase, depending on the studies.

1.4.1.2. Chair time

The paper by De Cock et al. defines chair time as "time between entry and exit of patient chair". The study concluded that SC administration provided a statistically significant decreased chair time. They were equal to 1h07 and 4h22 for SC and IV administrations. All studies comparing patient chair time between SC and IV rituximab reached the same conclusion: patient chair time was significantly decreased with SC rituximab [19,24,28].

The paper by Franken et al. concluded that "most studies reported a reduction between 68 and 78% for patient chair time" with SC administration [30].

1.4.1.2.1. Hospital perspective

A reduced chair time benefits the hospital. It enables to receive a higher number of patients each day and thus to decrease waiting lists. As mentioned rightly in the paper by De Cock et al., "rituximab SC administration, therefore, offers the potential to enhance the efficiency of oncology units and improve convenience for patients" [21,24,26].

According to the SCuBA study, addressing the benefits of SC administration of rituximab in 36 units in France, compared to the intravenous route, "the mean duration of occupation of a chair was reduced by 73.8 % for a session of subcutaneous rituximab". Thanks to that, the number of additional sessions possible per year increases, enabling to provide more chemotherapy sessions and thus to increase annual earnings [31].

A Canadian study wanted to apply the SCuBA study to Canadian cancer centers, and it arrived at the following conclusion: "the comparable efficacy, significant time and cost savings, and preference for the SC over the IV formulation of rituximab suggest that to increase efficiency in cancer care delivery, cancer centers should consider SC administration". Even if that study addressed FL, CLL, and diffuse large B cell lymphoma (DLBCL), the conclusion should be considered. Nevertheless, their study only focused on the costs associated with the injections and did not put the costs of rituximab in the balance, whereas, in the case of our study, the cost of the injection is the "starting point" [19].

1.4.1.2.2. Patient perspective

If the chair time is reduced, it benefits also the patient. For some patients, it represents a huge burden to have to go to the hospital. They feel they are wasting their time. It could impact their quality of life and well-being.

1.4.2. Differences related to costs

Sor far, this paper detailed about time savings, what is obviously linked to costs savings, like the well-known quote said, "time is money". It seems logical that if, for example, a pharmacist spent two times more time preparing an IV injection, in comparison with the formulation, that represents a doubled cost for an IV injection. In addition, material cost is different according to the formulation administered.

1.4.2.1. Pharmacists' salary cost

Concerning drug preparation, it has been found in the microcosting study by Mihajlovic et. al., that pharmacists' salary costs were 2,89€ and 2,70€ to prepare IV and SC injection respectively. In the SMABcare study, preparation times were longer, with salary costs associated of 9,30€ and 3,60€ [25,27].

1.4.2.2. Nurses' salary cost

Nurses' salary cost associated with each formulation is contested since nurses' time is controversial. In the SMABcare study, the total process in which a nurse is involved was longer in the case of an IV administration with salary costs of 12,60€ for the IV formulation and 6,30€ for the SC one. On the contrary, in the microcosting study by Mihajlovic et. al., it is mentioned that an IV administration requires less involvement of nurses, which is associated with a smaller nurse salary cost [25,27].

1.4.2.3. Materials cost

Materials used for an IV or a SC administration are different. The cost of materials associated with IV injection is higher than its associated with SC injection: 5,40€ vs 1,38€ in the paper by Mihajlovic et. al. In the SMABcare study the difference was greater: 11,0€ vs 0,51€ [25,27].

1.4.2.4. Patient chair time cost

As seen above, patient chair time is different depending on the formulation used. It is longer in the case of an IV administration. The costs associated with patient chair time are different according to the perspective taken.

1.4.2.4.1. Hospital perspective

The more patients spend time in the hospital, the fewer patients the hospital can take care of, which represents a loss of earnings for the hospital. This point will be discussed further.

1.4.2.4.2. Society perspective

The study by Franken et al. concluded that SC administration enables to reduce patient chair time and HCP time, compared to IV administration, resulting in "lower healthcare and lower societal costs". If a SC injection requires less time than the IV one, it means that patients may be able to go back to work faster. Thus, that could lower societal costs associated with patients in treatment. This point will not be discussed further as the perspective of society is not the subject of this project [30].

1.4.3. Other considerations

So far, only time and cost savings have been discussed. Nevertheless, other considerations are important: the BSA and the cost of the drug. It is important to analyze the costs associated with each formulation but also to take into account the cost of the drug (which is influenced by the BSA of the patient) and the discounts that could be proposed.

A sensitivity analysis performed in the SMABcare study showed that "it would be less expensive for the hospital to use the IV formulation in two cases: for people with small body surface area and if the purchase price of IV rituximab further decreases, as expected with the advent of biosimilar forms" [27].

1.4.3.1. Body surface area

The body surface area (BSA) is defined in the book "Pediatric Oncologic Pharmacy" as "a mathematical relationship, expressed in m^2, with the result obtained from the height and weight of the patient. This measure is used in order to obtain a more comprehensive parameter of the patient's weight, to define more appropriate dosage. The BSA is widely used in oncology, and the majority of protocols specify the dose in m^2". Thus, this is an essential measure for the calculation of the administered dose [32].

Concerning maintenance therapy of MCL with rituximab, BSA is important to calculate the dose when it is an IV injection (since the dose is fixed for an SC administration). It means that, if the patient is small and slim, the IV dose will be smaller. Thus, the cost of the drug will also be smaller. Whereas, if the patient is tall and overweighted, the dose is more important and the cost of the drug also. Some examples:

Patient with a BSA equal to 1,6 m^2: the dose required is 600 mg. The approximate drug costs are 1200€ and 1400 € for the IV and the SC formulations respectively.

Patient with a BSA equal to 2,2 m^2: the dose required is 825 mg. The approximate drug costs are 1750€ and 1400 € for the IV and the SC formulations respectively.

So far, it can be noticed that all the differences in terms of time and cost are in favor of the SC formulation, except nurse time which is controversial. Nevertheless, the cost associated to these time savings are very small in comparison to the cost of rituximab. If the small differences between both formulations are summed, it represents an almost trivial cost compared to the cost of the drugs.

However, as just said, for small and thin patients, IV formulation could appear more interesting, whereas, for tall and overweighted patients, SC rituximab could appear more interesting. The cost associated with the administration of rituximab could, in some cases, tilt the balance towards one formulation or the other. For example, when the BSA of the patient is not especially small and thin to conclude that IV rituximab is more advantageous in terms of cost, but not especially tall and overweighted to conclude that SC rituximab is more advantageous for him in terms of cost. We said already that the ex-factory price of one IV administration ranges from 1 191,48€ to 1 787,22 €. For this patient, the cost of IV rituximab could be close to the cost of SC rituximab. In this case, the "small" costs associated to the administration could tilt the

balance toward one formulation or the other. So far, no studies such as this one has been carried out.

1.4.3.2. Cost of the drug

The cost of a drug is a complex item. Sor far, the ex-factory costs were presented. But they are not the exact cost applied to each hospital. The ACAH is a negotiation center for hospital purchases. That is an association of hospitals of which the CHU-UCL Namur is a member. The ACAH issued an invitation to tender within the framework of a public contract. The company that won this contract, based on a number of criteria (involving quality and price), supplies the CHU-UCL Namur with the rituximab IV at a much lower cost than the ex-factory one. But this isn't the cost that is applied to all hospitals.
Each hospital association makes its own specifications, the companies respond with offers based on consumption, etc... It means that, since the development of the IV biosimilar, the CHU-UCL Namur hospital has a discount negotiated on the IV formulation but it is not the case for all hospitals. When the discount applied to the CHU-UCL Namur is taken into account, it is obvious that the most interesting formulation in terms of cost saving is the IV one.
Nonetheless, the aim of the study is to extent its utility to other hospitals that may or may not have a discount.

Consequently, in addition to what was just said, in the section about the BSA, about the importance to consider both the BSA of patients and the cost associated with rituximab administrations, it is also important to consider the exact cost of drugs and the discounts that could be applied. So far, no studies such as this have been carried out.

1.4.4. Patient preferences

It could be thought that patients will prefer SC injection given that they have to spend less time in the hospital since the administration time is shorter. But is it what patients really think? What about their satisfaction whit both administration ways? As rightly said in the paper by Fargier et al., about the SMABcare study, "quality of life and the patient's perception and preferences become relevant when treatment efficacy is equivalent, especially in oncology, where the goal is not only to cure or prolong survival but also to preserve the quality of life" [27].

When the question about formulation choice is asked to patients, they appear to prefer SC administration. The PrefMab study investigated the question in 2017. Two parameters were assessed: patient preference and patient satisfaction. In total, more than 700 patients were included in the study population. Concerning patient preference, the results were clear, the majority of the patients had a "strong" or a "fair" preference for SC administration. The main reasons behind this preference were: "requires less time in the clinic", "feels more comfortable during administration", "feels less emotional distressing" and "lower level of injection site pain" [33].

This study was performed in patients receiving rituximab for the first time, to treat FL or DLCBL. Patients' preferences didn't seem to be impacted by the lymphoma type, thus, even though this study was performed with patients affected by other lymphomas, the results can be extrapolated. The general conclusion was that patients had a strong preference for SC administration, but the paper cites: "considering rituximab SC was administered in a clinical setting as part of a treatment regimen that contained an IV chemotherapy component". The same conclusion about SC preference has already been drawn in the PrefHer study concerning IV or SC administration of Trastuzumab for patients affected by HER2-positive early breast cancer [33].

The SMABcare study performed in 2017 with 73 patients affected by FL, had a second objective to study the health-related quality of life and the preferences of patients and nurses concerning maintenance therapy, in France. This patient preference for SC administration was confirmed, 69% of patients prefer SC administration (only 5% favor the IV administration and the others have no preference). The main argument explaining this preference was "time savings" but also, as said in this paper "making cancer less alarming: with no IV port hanging out, it seems less serious", "less technical procedure", "a simple SC injection is less bothersome and less scary" and "the port can be removed". Nevertheless, some trends emerge with, on the one hand, a preference for SC injection in order to decrease anxiety and depression but, on the other hand, a preference for IV injection concerning pain and discomfort during injection. Those trends would need further investigations [27].

Concerning nurses' preferences and satisfaction, the results must be considered carefully because of the small number of nurses involved in the study. According to them, SC administration seems to be better tolerated and reduces day unit stay and consumable use [27].

1.4.4.1. Health-related quality of life (HRQoL)

HRQoL comparing IV and SC rituximab had only been assessed in the SMABcare study which concluded that "the evaluation of health-related quality of life on the EQ-5D-3L questionnaire revealed no significant difference between the two groups" [27].

1.4.4.2. Patient satisfaction

Concerning patient satisfaction, when assessed by the Cancer Treatment Satisfaction Questionnaire (CTSQ), scores were the same concerning both administration routes. Nevertheless, when assessed with the Rituximab Administration Satisfaction Questionnaire (RASQ), patients were more satisfied with SC rituximab for "psychological impact", "impact on activities of daily living", "convenience of therapy" and "satisfaction with therapy" [33].

The conclusion concerning patient satisfaction is more nuanced than concerning patient preference. When assessed with the CTSQ, patient satisfaction is the same in both groups, as already concluded in the MABEASE study in patients with DLBCL. But, when assessed with the RASQ, patients are more satisfied with SC administration of rituximab, as also already concluded in the MABEASE study [33].

1.5. Summary of advantages and disadvantages of both forms

The next sections present summary of time saving, cost saving and patient preference, satisfaction, and HRQoL.

1.5.1. Summary of time saving

The main points in favor of SC injection in terms of time saving are a decreased preparation time, a decreased administration time, and shorter chair time. Concerning nurse time, it is controversial. Concerning IV formulation, all points seem to be at its disadvantage except the nurse time which could be decreased depending on the source (see table 1).

Table 1: Summary of the times involved with each formulation.		
	Intravenous	Subcutaneous
Drug preparation	Patient-dependent dose (risks of dose calculation errors) → longer preparation time	Fixed dose (decreased dose calculation errors) → shorter preparation time
	No limitation of drug volume	Limitation of drug volume
	➔ Decreased active HCP time with SC administration	
Administration time	Longer administration time	Shorter administration time
	Faster workflow for medical staff?	Slower workflow for medical staff?
	➔ Decreased administration time with SC but possible increased nurses' time.	
Chair time	Longer administration time	Shorter administration time
	➔ Decreased chair time with SC administration	

1.5.2. Summary of cost saving

Concerning the costs involved, all the costs associated with rituximab administration are in favor of the SC formulation, except the controversy on nurse time (see table 2). Drug cost depends on the BSA of the patient. If a patient is small and slim, the IV dose will be small. Thus, the cost of the drug will be smaller than the cost of one SC injection. Whereas, if the patient is tall and overweighted, the dose is more important and the cost of the drug also. For him, it will probably be cost saving to use the SC formulation.

Table 2: Summary of the costs involved with each formulation.		
	Intravenous	Subcutaneous
Administration associated costs (drug preparation, administration time, chair time, materials)	Longer pharmacists' involvement	Shorter pharmacists' involvement
	Shorter nurses' involvement?	Longer nurses' involvement?
	Longer chair time	Shorter chair time
	Higher materials cost	Lowest materials cost
	➔ Lower costs with SC administration	
Drugs costs	IV rituximab influenced by the BSA of the patient → Variation in drug cost	

1.5.3. Summary of patient preference, satisfaction and HRQoL

Patients have a preference for SC rituximab. Concerning their satisfaction with the treatment, the results were the same in both groups. Finally, so far, there is no significant difference between both an IV and a SC formulation concerning HRQoL.

1.6. Choice of analysis type

The type of analysis chosen was first a pharmacoeconomic study. Then, it has been decided that a BIA was more appropriate, as explained below.

1.6.1. Introduction to pharmacoeconomic

In the beginning, it was planned to perform a pharmacoeconomic analysis. According to the book "Introduction à la pharmacoéconomie" by A. Crochard-Lacour et al., "a pharmacoeconomic analysis is an economic evaluation in which at least one of the options

studied is pharmacological in nature. Like health economics, pharmacoeconomics identifies, measures and compares costs (resources consumed) and consequences (benefits, advantages, etc.)." [34].
The costs to take into account in the analysis aren't just "direct costs", such as the costs of the injection for example, because there are also "indirect costs". An example of indirect costs could be the productivity decline of a patient concerning his job, because of a long hospital stay, linked to the injection [35].

1.6.1.1. From pharmacoeconomic analysis to a budget impact analysis

What is very important to consider is that, when a pharmacoeconomic analysis is conducted, parameters other than costs must be taken into consideration, such as quality of life, satisfaction, return to work, … But unfortunately, since the study is a retrospective study, it wasn't possible to study those parameters afterward and that is the reason why, a change in the type of analysis has been carried out, moving from a pharmacoeconomic analysis to a budget impact analysis (BIA).

1.6.2. Budget impact analysis

A BIA is a cost study that can be performed in order to know the impact, in terms of costs, of the implementation of a new treatment. This analysis can be done by health care providers themselves, willing to analyze the consequences of adopting a new health care intervention. Performing a BIA enables to summarize all the information and costs known on different treatments, in order to make the best decision when choosing to administer a new health care intervention instead of another [36].

Most of the time, the results of a BIA are applicable to a specific location like a group of hospitals or a specific area. This is explained by the fact that, for example, for a specific treatment, each hospital will have a specific negotiated price with the firm. That is explained in the paper by Sullivan S. et al., "Given the systems' highly local nature and decision-makers' varying perspectives, a BIA cannot give a single estimate applicable to all decision-makers. Instead, the purpose of a BIA is to provide a valid computing framework—a "model"—that allows users to apply input values and view financial estimates pertinent to their setting" [36].

Thus, this BIA will be specific to the CHU-UCL Namur site, even though particular attention will be given to extrapolate the results to other settings. That is why several scenarios will be considered, with several discounts. A BIA aims to provide answers to several questions asked by a specific institution. Those questions are switched into a hypothesis to which the model used will give answers [36].

In a BIA, different aspects have to be taken into account. The first aspect is the perspective. In this case, it will be the hospital which is the CHU-UCL Namur. Obviously, the use and cost of the current and new intervention, which are IV and SC rituximab, will be part of the analysis. Given that there are not only the costs of the drug but other costs that have to be taken into account, impact on other costs will be also studied like the time and the cost of nurses, pharmacists, the cost of materials, … The final aspect to take into account before performing a BIA is the hypothesis that will be tested [36].

2. Aims of the research

Previous studies demonstrated the biosimilarity between IV and SC rituximab. Both formulations are equivalent and are administered in maintenance therapy of MCL. The goal of this research is to identify the most interesting formulation of rituximab (between IV and SC) economically speaking. For this purpose, there is not only the cost of the drug to take into account, but also other non-drug costs related to rituximab administration like the salary cost of the nurse to administrate the drug, the salary cost of the pharmacist to prepare the drug, the material costs, …
A lot of studies have already demonstrated the advantages of SC administrations in terms of time and cost savings. But none of those studies took into account at the same time the cost of rituximab, the potential discounts that could be proposed, the influence of the BSA, and non-drug associated costs. The potential discounts and the influence of the BSA are the two additional considerations that have been taken into account in the present study, in comparison with previous studies.

- Potential discounts: several scenarios with different possible discounts were studied.
- Influence of the BSA: as already said, the cost of the treatment depends on the dose administered, which depends on the BSA of the patient. Therefore, a distinction between patients with different BSA has been done.

The primary goal was therefore to find, with each discount, which way of administration is the most advantageous, depending on the BSA of the patient.

A secondary goal was to focus on the real-time spent by patients in the hospital.

3. Methods

This study was a retrospective observational study. Patients included were treated in CHU-UCL Namur, which constituted a monocentric study. For ethical concerns, the protocol has been submitted to the Ethics Committee.

3.1. Patient population

48 courses of IV administration versus 50 courses of SC administration were compared. Rituximab had been administrated to a population of 13 patients in maintenance therapy of MCL. Out of these 13 patients, 8 patients included in the MCL-R2 study (EUDRACT number: 2012-002542-20) received SC rituximab, and 5 patients received IV rituximab according to routine medical practice. The number of infusions per patient ranged from 2 to 12.
Patients were 18 years old or more, men or women, and had a biopsy-proven MCL. All patients have been treated at a single institution, CHU-UCL Namur hospital, Yvoir between March 2015 and September 2020.

There were no exclusion criteria.

3.2. Data collection

First, the clinical characteristics of all patients included in the study and some data related to Belgians in general were collected. After that, the goal was to focus on 50 administrations of rituximab in the SC group and 48 administrations in the IV group in order to collect patient time in the hospital. Drug preparation and administration times were collected. In addition, data related to cost like salary costs, material costs and drugs cost were collected.

Both for IV and SC rituximab, data were collected from maintenance therapy of MCL lymphoma in order to collect data from patients who had only received rituximab and not rituximab associated with chemotherapy, which could have influenced several criteria like times or the status of the patient.

Concerning data sources, the data were collected at the Yvoir site of the CHU-UCL Namur and, regarding inputs data for which there were no available data for the Yvoir site, literature was taken into account.

3.2.1. Patient clinical characteristics

As said before, not only data related to time and cost were collected. Clinical characteristics of the 13 patients in CHU-UCL Namur were collected but also data related to Belgians in general. Those data available for Belgians were used to carry out the BIA.
It has been decided to do so for the reason that, the BIA aims to identify which treatment is the most interesting economically speaking. Thus, that took into account BSA, which is patient-dependent. If the calculations are made based on the data of the CHU-UCL Namur population, it will not reflect the reality in Belgium. Moreover, it could have created a bias since the CHU-UCL Namur population is small. In order to avoid bias and to extend the study results to the whole of Belgium, data considering Belgians on average were considered.

The clinical characteristics collected were the following: the gender, age, weight, height, BSA, and the stage of the disease at diagnosis. The MIPI score was calculated at diagnosis.

Also, the performance status and the lactate dehydrogenase (LDH) level were collected at each injection.

3.2.1.1. General clinical characteristics

The age, the weight, and the height of the patient were taken at diagnosis.

3.2.1.2. BSA

The BSA of each patient was collected, as it influenced the dose of the drug.

3.2.1.3. Stage of the disease

The stage of the disease ranged from I to IV, depending on the spread of the disease in the body.

3.2.1.4. MIPI score

The MIPI score is the mantle cell lymphoma international prognosis index. MIPI is a prognosis index of overall survival for patients with an advanced stage of MCL. This index is calculated based on 4 independent prognosis factors: age, performance status, LDH level, and leucocyte count. This score enables to classify patients into low-risk, intermediate-risk, or high-risk groups. As said in the paper by Hoster et al., "the MIPI is the first prognostic index particularly suited for MCL patients and may serve as an important tool to facilitate risk-adapted treatment decisions in patients with an advanced stage MCL" [37].
MIPI scores were calculated at the time of the diagnosis.

3.2.1.5. Performance status

The performance status is defined by the National Cancer Institute as "a measure of how well a patient is able to perform ordinary tasks and carry out daily activities". This status ranges from 0 (the patient is fully active) to 5 (death) and is used to evaluate how the disease and the treatment impact daily activities, condition, and abilities of the patients [38].

3.2.1.6. Lactate dehydrogenase

Finally, the LDH level is known as a tool used to evaluate the efficacy of a treatment in patients with cancer like MCL. A paper by Forkasiewicz et al. published in June 2020 explained: "One of the hallmarks of cancer cells is increased energy requirements associated with the higher rate of cellular proliferative activity". The increasing activity requires increased uptake of glucose which can be observed and reflected by a higher level of serum LDH "which regulates the processing of glucose to lactic acid". And the paper adds "as serum LDH levels were found to be commonly increased in cancer patients and correlated with poor clinical outcome and resistance to therapy, the determination of LDH has become a standard supportive tool in diagnosing cancers or monitoring the effects of cancer treatment" [39].

3.2.2. Input variables

Input variables included in the BIA were data related to time and data related to cost.

3.2.2.1. Data related to time

Different data related to time were collected: drug preparation and pharmacist's involvement, and administration time and nurse's involvement.

3.2.2.1.1. Drug preparation and pharmacist involvement

To know drug preparation time and then to evaluate the costs associated with pharmacists' involvement, a pharmacist of the CHU-UCL Namur, Yvoir site was contacted.

3.2.2.1.2. Administration time and nurse involvement

To know as precisely as possible, the time of nurses' involvement, the head nurse of the day hospital of the CHU-UCL Namur, Yvoir, was contacted. The final aim was to know how much time nurses were involved in the process.
Different times concerning each injection were available:

- Patient's arrival in the hospital
- Patient's installation in the room
- Patient perfused
- Treatment ordered in pharmacy
- Start of the injection
- End of the injection
- Patient's discharge from hospital

Those times were very prone to inaccuracies because it was the nurse which has to encode all those times in a database. Sometimes the times weren't encoded directly and are, thus, incorrect. Only two times were always correct. The first one is the patient's arrival, because nurses have to encode that the patient arrived in the hospital. The second time which was always accurate is the start of the injection because nurses had to clock in the time to start the administration.

Taking times inaccuracies into account, there were two different ways to obtain the administration time:

- The first way was to use times encoded. The difference between the time of the end of the injection and the time of the start of the injection gave the administration time, but some inaccuracies could exist concerning the time of the end of the injection.
- The second way was to use only the theoretical administration time as mentioned in the SmPC.

This second way of working was more accurate and that is why it was decided to work as explained in the second case in order to avoid inconsistencies and encoding issues as much as possible.

3.2.2.2. Data related to cost

Several data related to cost were collected: salary costs, drugs costs, materials costs, and patient chair time cost.

3.2.2.2.1. Salary costs

Salary costs of pharmacists and nurses entered in the analysis. Those data came from the human resources department of the CHU-UCL Namur.

3.2.2.2.2. Drugs costs

In order to get the ex-factory cost of drugs, the pharmacy department of the CHU-UCL Namur, Yvoir was contacted. As mentioned before, the negotiated price of the CHU-UCL Namur couldn't be disclosed, that is why the study was performed based on the ex-factory costs which were the same for all hospitals in Belgium.

3.2.2.2.3. Materials costs

The costs of the materials needed for each injection were collected. Those costs were given by a hospital pharmacist of the CHU-UCL Namur, Yvoir site.

3.2.2.2.4. Patient chair time cost

Concerning patient chair time cost, three main perspectives could be evaluated: the hospital perspective (so the cost that represented patient chair time for the hospital), patient perspective, and societal perspective. Given the fact that the BIA took the perspective of the hospital, the first one was considered.
In fact, patient chair time cost taking the perspective of the hospital could be reflected by day care treatment cost, which was collected.

3.2.3. Data selection and data exclusion

Since March 2015 and until September 2020, 16 patients have been treated for MCL in CHU-UCL Namur. Among those 16 patients, only 13 began maintenance therapy and thus could be included.
Concerning unknown data for the CHU-UCL Namur, the data were taken from the literature. This data extraction of the literature was performed in order to have all the data available to perform the analysis. Importantly, it was done with the concern to meet as precisely as possible the reality.

3.3. Budget impact analysis

The BIA was performed based on an economic model provided by Mundipharma, a pharmaceutical company. The model had been developed by Dr. Pieter Dylst PhD in Pharmacy when he worked for Mundipharma as Head of market access and biosimilars. Annex 1 presents some papers written by Dr. Pieter Dylst.

3.3.1. Perspective

The perspective according to which the analysis was done was the hospital.

3.3.2. Analytic framework description

The computing framework used in the present study was a simple Excel spreadsheet containing a cost calculator, supplied by Mundipharma. The spreadsheet was divided into 2 sheets: input variables and economic model (presented in annex 2).

3.3.3. Input data

As said, the first sheet contained the input variables which are presented in table 1 below. The input variables were of two types: data related to cost or data related to times, as detailed previously. The data source of each input variable is also mentioned.

Table 1: Description of the input variables contained in the first sheet of the calculator

Type of data	Input variables	Data source
Data related to cost	Salary cost	HR Department of CHU-UCL Namur
	Drug cost	Fixed ex-factory price for all hospitals in Belgium
	Material cost	Pharmacy Department of CHU-UCL Namur
	Patient chair time cost (day care treatment cost)	CHU-UCL Namur
	Drug preparation time	CHU-UCL Namur

Data related to time	Administration time	Theoretical administration and observation times as recommended in the SmPC.
	Nurse involvement	Mihajlovic et al., 2017.

HR = Human Resources

3.3.4. Economic model

The economic model was divided into 4 sections:

- Treatment regimen
- Number of vials needed
- Price calculation without discount
- Price calculation with discount

3.3.5. Hypothesis

Since the dose of rituximab was BSA-dependent, the cost of one injection was different for each patient. The aim was to find a tipping point in BSA. This tipping point could be defined as followed; that was the BSA value, beyond which it is more interesting to use the SC formulation and below which it is more interesting to use the IV formulation.

Different situations could occur:

- First, the tipping point could be in a realistic range of BSA. Below this tipping point, it was more interesting to administrate the IV formulation and above, the SC form.
- Another possibility was that the tipping point was so high that made it unrealistic. In this case, it was always more interesting to use the IV form.
- The last possibility was that the tipping point was so low, that made it also unrealistic. But in this case, that meant it was more interesting to use the SC form.

After that, a comparison between this tipping point and the mean BSA of Belgians was done in order to conclude which formulation was the most interesting in routine medical practice.

3.3.5.1. Application to routine medical practice

The results found so far showed a tipping point BSA below which it was cost savings to administrate IV rituximab and above which it was more interesting to administrate SC rituximab. Nonetheless, it is important to mention that in routine medical practice, all the patients receive the same formulation, either SC or IV. HCP doesn't change the administration way for each patient, depending on their BSA. Meaning that, the conclusion about the formulation which was the best economically speaking concerned all the patients, even those with a BSA for which the other formulation would be more interesting.

In order to conclude on the formulation which had to be used in routine medical practice, the tipping point was compared to the mean BSA of Belgians. Two scenarios were possible:

- The tipping point was below the mean BSA of Belgians. It meant that for a majority of Belgian patients it was cost savings to administrate the SC formulation.
- The tipping point was above the mean BSA of Belgians. It meant that for a majority of Belgian patients it was cost savings to administrate the IV formulation.

Different tipping points were found, depending on the discounts applied to IV and SC rituximab.

3.3.6. Model validation

The model has still to be validated. It was the first time it was used. Thus, the validation has still to be done, since a model validation has to be performed after having used the model for the first time.

3.4. Patient time

The BIA took into account the hospital's perspective. Given that, the perspective of the patient didn't enter the analysis. This additional point aimed to focus on time saving for the patient. The aim was to analyze the time spent by patients in the hospital for IV and SC administration.

As defined before, the chair time is the "time between entry and exit of patient chair". In other words, it was the difference between the end of the injection (for IV administration) or the end of observation time (for SC administration) and the time at which the patient is installed in the room. Thus, patient chair time could be calculated by making the difference between those times. Nevertheless, these times were very prone to inaccuracies. Thus, patient chair time couldn't have been calculated with a minimum of accuracy.

Therefore, in order to have a global overview of the time spent by the patient in the hospital, that wasn't the chair time which was calculated but the total time patient spent in the hospital. This patient time was calculated by making the difference between the theoretical end of injection (IV) or observation time (SC) (which was the start of injection plus the administration times like recommended in the SmPC) and the arrival of the patient (which was accurate).

3.5. Statistical analysis

BIA statistics and patient time statistics were performed.

3.5.1. BIA statistics

Concerning patient clinical characteristics, continuous values were described by the mean and the standard deviation (SD). The parametric values were described by proportion (percentage).

3.5.2. Patient time statistics

Mean time spent in the hospital and SD were calculated. Equivalence of the variances was tested before performing a student test in order to compare the mean of each group.

4. Analysis

4.1. Patient clinical characteristics

Clinical characteristics of the CHU-UCL Namur population and of Belgians were collected.

4.1.1. Description of the CHU-UCL Namur population

Among the 13 patients included in the study, men represented 69% of all the patients. The mean age at diagnosis was 65 years. The median age was 69 years (38-77 years).
Concerning the weight and the height, the mean values were 80,38 kg (80,38 ± 17,03) and 171cm (171 ± 13,27). The mean BSA was 1,92 m^2 (1,92 ± 0,24).

For the next clinical characteristics, there were some unknown data. The description of the population was done according to the known values.
About the stage of the disease, 75% of the patients presented a stage IV MCL. At diagnosis, all the patients for which performance status had been recorded had a performance status of 0-1. During maintenance therapy, this percentage lowered to 89%.
Concerning LDH level, approximately 15% of the values were above the standard at diagnosis. During maintenance therapy, this percentage lowered to 5%.
About known MIPI scores at diagnosis, 58% of patients had a MCL of intermediate-risk, 25% high-risk, and 17% low-risk (see table 1).

Table 1: Description of the CHU-UCL Namur population affected by MCL. The number of patients was 13 and the number of rituximab maintenance therapy injections was 98.

		Mean ± SD (median + range)	Proportion + percentage
Gender	Men (n; %)		9/13; 69,23%
	Women (n; %)		4/13; 30,77%
Age at diagnosis (years)		64,92 ± 11,70 69 (38-77)	
Weight at diagnosis (kg)		80,38 ± 17,03	
Height at diagnosis (cm)		171 ± 13,27	
BSA at diagnosis(m^2)*		1,92 ± 0,24	
Stage of the disease at diagnosis	Unknown values (n)		1/13*[2]
	Known values (n)		12/13
	I (n;%)		0/12; 0%
	II (n;%)		1/12; 8,33%
	III (n;%)		2/12; 16,67%
	IV (n;%)		9/12; 75%
Performance status at diagnosis	Unknown values (n)		1/13*[2]
	Known values (n)		12/13
	0-1 (n;%)		12/12; 100%
	≥ 2 (n;%)		0/12; 0%
Performance status during maintenance therapy	Unknown values (n)		25/98*[3]
	Known values (n)		73/98
	0 - 1(n;%)		65/73; 89,04%
	≥ 2 (n;%)		8/73; 10,96%*[4]
LDH level at diagnosis	Unknown values (n)		1/13*[2]

	Known values (n)		12/13
	Value in or below the standard (n;%)		10/12; 83,33%
	Value above the standard (n;%)		2/12; 16,67%
LDH level during maintenance therapy	Unknown values (n)		3/98*[5]
	Known values (n)		95/98
	Value in or below the standard (n;%)		90/95; 94,74%
	Value above the standard (n;%)		5/95; 5,26%
MIPI score	Unknown values (n)		1/13*[2]
	Known values (n)		12/13
	Low risk (n;%)		2/12; 16,67%
	Intermediate risk (n;%)		7/12; 58,33%
	High risk (n;%)		3/12; 25%

* BSA calculated with the Dubois formula.
*[2] One missing data since one patient was not treated at CHU-UCL Namur at the date of the diagnosis.
*[3] Performance status during maintenance therapy is not reported systematically.
*[4] Out of the 73 performance status known, there were 36 in the IV group and 37 in the SC group. In the IV group, only 1 data was ≥ 2 whereas, in the SC group, 7 data were ≥ 2.
*[5] Out of 98 injections, 3 LDH levels were unknown due to a hemolysis sampling.

4.1.2. Description of the Belgian general population

In the Belgian general population, there is approximately 50% of men and 50% of women. The mean BSA of Belgians is 1,84 m^2. The mean BSA of men in Belgium is 1,99 m^2 and the mean BSA of women in Belgium is 1,74 m^2 (see table 2).

Table 2: Description of the Belgian population affected by MCL.

		Mean	Percentage
Gender	Men (%)		50%*
	Women (%)		50%
Weight (kg)	Men	80,1	
	Women	66,4	
Height (cm)	Men	177	
	Women	164	
BSA (m^2) *[2]	Overall	1,84	
	Men	1,99	
	Women	1,74	

The Belgian data originated from Sabine Drieskens, a scientist in epidemiology and public health at Sciensano.
* Estimated percentage.
*[2] BSA calculated with the Dubois formula.

4.1.3. Belgian population affected by MCL

The general Belgian population is not the same as the Belgian population affected by MCL. In Belgium, there are approximately half men and half women. But that is not the same proportion in patients affected by MCL since men are two to three times more affected than women. Thus, the mean BSA of Belgian affected with MCL is not the same as the mean BSA of Belgians. For

this reason, the mean BSA of Belgians affected by MCL was calculated in order to get a more precise value. The calculation was done taking the fact that men are two to three times more affected than women into account, as followed:

- Men are 2 times more affected → Men represent 66,67% of patients affected by MCL
- Men are 3 times more affected → Men represent 75% of patients affected by MCL

Thus, on average, men represent 70,84% of patients affected by MCL. Women represent 29,16% of patients affected by MCL. What was approximatively the same proportion as seen in the CHU-UCL Namur population (69,23% and 30,77%)

→ Calculation of the mean BSA: (70,84%x1,99m^2 + 29,16%x1,74m^2)/100% = 1,92 m^2

Then mean BSA of Belgians affected by MCL was equal to 1,92 m^2. That was the same value as the mean BSA of the CHU-UCL Namur population.

4.2. Input variables

Data related to time and data related to cost were collected.

4.2.1. Data related to time

Drug preparation time and the duration of pharmacist involvement were collected.

4.2.1.1. Drug preparation and pharmacist involvement

IV preparation time was evaluated by Decoster C., hospital pharmacist at CHU-UCL Namur. This time was equal to 294 seconds for one injection. Concerning SC preparation time, it was different since this formulation didn't require any time to prepare. It was the nurse which has to extract and then directly inject the drug. Therefore, SC preparation was equal to 0.

4.2.1.2. Administration time and nurse involvement

As explained before, theoretical administration times were used in the present study. Those were 90 min and 5 min (+15 min observation time) for IV and SC rituximab respectively, according to SmPC.

Concerning nurses' involvement, it appeared that nurse's solicitation differences between both groups only concerned the administration time. Collecting exact nurses' involvement time for each injection had not been possible retrospectively. Nurses' involvement time wasn't known at CHU-UCL Namur hospital and was taken in the literature. In a paper by Mihajlovic et al., it has been reported that mean nursing times were 13,65 min and 16,50 min for one IV or SC administration, respectively. Nurses of CHU-UCL Namur agreed they spend more time when it was an SC administration than with an IV administration. With an SC administration, they had to care for the patient during all the administration time whereas it wasn't the case when it was an IV administration [25].
Thus, even if the administration time was longer for an IV injection in comparison with a SC injection, nurses' involvement was longer for SC administration.

4.2.2. Data related to cost

Salary costs, drug costs, materials costs, and patient chair time cost were collected.

4.2.2.1. Salary costs

The salary costs for HCP at the CHU-UCL Namur were the followings:

- Pharmacist: 30,04€/h (13 years seniority) or 0,50€/min.
- Pharmacy assistant: 16,04€/h (9 years seniority) or 0,27€/min.
- Nurse: 19,02€/h (9 years seniority) or 0,32€/min.

Even though salary costs depended on the seniority, the analysis was done taking into account those salary costs for all the administrations.

4.2.2.1.1. Pharmacists' salary cost

Taking into account drug preparation times, pharmacists' salary costs were equal to 2,45€ for IV administration and equal to 0€ for an SC administration, for one rituximab injection. The BIA took into consideration the salary cost of the pharmacist and not this of the assistant. In this case, the salary costs would have been equal to 1,32€ and 0€.

4.2.2.1.2. Nurses' salary cost

Taking into account nurses' involvement times in the paper by Mihajlovic et al., nurses' salary costs were equal to 5,23€ for SC and 4,33€ for IV rituximab, for one rituximab injection.

4.2.2.2. Drugs costs

The ex-factory cost was the cost considered in this study. An ex-factory cost is the cost minus the value-added tax (VAT), what is the real cost for hospitals.
The ex-factory costs of the injections (costs as of October 2020) were the followings:

- SC rituximab: 1398,67€ for 1400mg
- IV rituximab: 198,58€/100mg for an IV administration

What was important to notice was that SC rituximab was supplied in vials of 1400 mg and IV rituximab was supplied in vials of 100 mg. The mean BSA of Belgians affected with MCL was 1,92 m^2. For such a patient, the IV required dose was 720 mg. Thus, 8 IV vials of 100 mg were needed (see below in section 3.2. Number of vials needed). Thus, for a mean Belgian the IV cost of one injection was 1586,64€ (8 vials x 198,58€).

The cost of the IV form was higher than the real cost applied in CHU-UCL Namur. As mentioned previously, hospitals have negotiated prices with pharmaceutical companies but the discounts are confidential and could not be revealed. For this reason, different scenarios with different discounts were considered.

4.2.2.3. Materials costs

Materials costs considered in the study were those of CHU-UCL Namur. The detail concerning each material and price can be seen in annex 3. In total, 16,86€ of materials were needed for an IV injection and 5,01€ for an SC one.

4.2.2.4. Patient chair time cost

Even though patient chair time was not the same with IV and SC rituximab, the day care treatment cost was the same for both formulations. In the CHU-UCL Namur, there was a fixed fee of 126,20€ for day care treatment, regardless of the time spent in the hospital. Consequently, here it didn't tip the balance from one way or the other since the price was fixed. This fixed fee

depended on the number of drugs the patient received. Here, whether it was IV or SC rituximab, it was still one drug.

4.2.3. Additional cost IV vs SC

In brief, the additional costs associated with the administration of rituximab were:

- Salary cost of nurses (related nursing time)
- Salary cost of pharmacists (related pharmacy preparation time)
- Material cost
- Patient chair time cost (day care treatment cost)

When all the costs associated with rituximab administration were summed, one IV administration represented an additional cost of 13,40€ (see table 3). Taking into account that maintenance therapy was constituted by 12 cycles as stated in the notice, it represented a total additional cost of 160,80€ for all the maintenance therapy.

Table 3: List of the costs associated with each administration type and the cost difference between both formulations.

Cost item	Cost of IV administration (€)	Cost of SC administration (€)	Difference IV - SC (€)
Cost of nurse	4,33	5,23	-0,90
Cost of pharmacist	2,45	0	2,45
Material cost	16,86	5,01	11,85
Patient chair time cost (day care treatment cost)	126,20	126,20	0
Total cost	149,84	136,44	13,40

The costs were those for only one single injection.

This additional cost of 13,40€ for one single administration was small in comparison to drug cost. It represented approximatively 1% and 0,85% of the cost of one injection of SC and IV rituximab.

4.3. Economic model

4.3.1. Treatment regimen

According to the standard of care based on clinical trials, patients received twelve injections of maintenance therapy. The dose was 375 mg/m^2 for IV administration and 1400 mg (fixed) for SC administration.

4.3.2. Number of vials needed

Concerning SC maintenance therapy, the dose was always 1400 mg. Thus, the number of SC vials needed for the 12 cycles was always 12 (see table 4).
With the treatment regimen, the dose needed by a patient according to his BSA was known. As said before, rituximab was supplied by vials of 100 mg. It meant that, if a patient needed 720mg of rituximab, 8 vials were needed (see table 4).
The following case took the example of a patient with a BSA of 1,92 m^2. For him, 8 IV vials of 100 mg were needed for 1 cycle, thus, 96 IV vials were needed for the 12 cycles. If it was the SC rituximab that was administered to him, 12 vials were needed for all the maintenance therapy (one vial of 1400 mg per cycle).

Table 4: Number of vials needed in case of IV or SC maintenance therapy, according to the BSA of patients.					
	IV maintenance therapy			SC maintenance therapy	
BSA (m^2)	IV dose (mg)	Number of IV vials of 100 mg for one cycle	Number of IV vials for the entire maintenance therapy (12 cycles)	SC dose (mg)	Number of SC vials of 1400 mg for the entire maintenance therapy (12 cycles)
1,34 – 1,60	502,50 – 600,00	6	72	1400	12
1,61 – 1,86	603,75 – 697,50	7	84	1400	12
1,87 – 2,13	701,25 – 798,75	8	96	1400	12
2,14 – 2,40	802,50 – 900,00	9	108	1400	12

The ranges of BSA presented in table 4 represented the minimum and the maximum BSA for which the number of IV vials was the same. Consequently, for patients in the same range of BSA, drug cost was also the same.
These values were found further in the tables as the tipping points. The tipping point was defined previously as the value of BSA below which it is less expensive to administrate the IV formulation and above which it is less expensive to administrate the SC form.

4.3.3. Cost calculation without discount

The following case illustrated a patient with a BSA of 1,92 m^2. The number of IV vials of 100mg needed for the entire maintenance therapy is 96. The cost of one IV vial of 100mg is 198,58€. Thus, the total drug cost for maintenance therapy with IV administrations, for this patient was 19 063,68€. For the same patient, the total cost of SC drugs for maintenance therapy was 16 784,04€ (12 vials x 1 398,67€).

When the cost of treatment for each formulation was calculated, the difference could be done. For an adult with a BSA of 1,92 m^2, the difference was 2 279,64€ (19 063,68€ - 16 784,04€). When the 160,80€ of savings through SC use were added to this difference, the total additional cost by using the IV form can be calculated and was equal to 2 440,44€.

Table 5 below showed the drug cost difference between IV and SC rituximab according to the BSA (only drug costs were taking into account in the second column). The third and the fourth columns illustrated the cost savings with one formulation or the other, taking into account the 160,80€ saved through SC use for all the maintenance therapy (as explained in section 2.3).

When there was no discount applied, it was less expensive to administrate the IV formulation up to patients with a BSA equal to 1,60 m^2 (see table 5). Above this value, there were some additional costs with IV rituximab in comparison with the SC formulation.

Table 5: Difference between IV and SC formulation and cost savings, according to the BSA. No discount is applied.			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	-2 486,28	/	2 325,48
1,61 - 1,86	-103,32	57,48	/

1,87 – 2,13	2 279,64	2 440,44	/
2,14 – 2,40	4 662,60	4 823,40	/

4.3.4. Cost calculation with IV discount

As mentioned previously, the exact drug cost of the IV biosimilar couldn't be disclosed. That is the reason why different scenarios concerning IV drug cost and so, discounts made on this IV form were evaluated.

4.3.4.1. Discount of 10%

When there was a 10% discount applied on the IV form, it was cost saving to administrate the IV formulation to patients with a BSA ≤ 1,86 m^2. Beyond this value, there were some additional costs with IV rituximab in comparison with the SC formulation (see table 6).

Table 6: Difference between IV and SC formulation and cost savings, according to the BSA. A discount of 10% is applied to the IV form.

BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 -1,60	-3 916,06	/	3 755,26
1,61 -1,86	-1 771,39	/	1 610,59
1,87 -2,13	373,27	534,07	/
2,14 - 2,40	2 517,94	2 678,74	/

4.3.4.2. Discount of 20%

With a 20% discount on the IV formulation, it was cost savings to administrate the IV formulation to patients with a BSA ≤ 2,13 m^2. Beyond this value, there were some additional costs with IV rituximab and SC rituximab became cost saving (see table 7).

Table 7: Difference between IV and SC formulation and cost savings, according to the BSA. A discount of 20% is applied to the IV form.

BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	-5 345,83	/	5 185,03
1,61 - 1,86	-3 439,46	/	3 278,66
1,87 - 2,13	-1 533,10	/	1 372,30
2,14 - 2,40	373,27	534,07	/

4.3.4.3. Discount of 30%

Considering a discount of 30% on the IV formulation (see table 8), it was less expensive to administrate the IV formulation to all patients, considering that almost no patient has a BSA above 2,40 m^2.

Table 8: Difference between IV and SC formulation and cost savings, according to the BSA. A discount of 30% is applied to the IV form.			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 -1,60	-6 775,61	/	6 614,81
1,61 - 1,86	-5 107,54	/	4 946,74
1,87 - 2,13	-3 439,46	/	3 278,66
2,14 - 2,40	-1 771,39	/	1610,59

4.3.5. Cost calculation with IV and SC discount

So far, only IV discounts had been taken into consideration. But the pharmaceutical company can sometimes propose a discount of up to 15% on the SC formulation. In the following part, the analysis was done taking into account the hypothesis of a 15% discount on the SC formulation.

4.3.5.1. No discount on the IV form and 15% discount on the SC form

Considering no discount on the IV form and 15% on the SC form, it was always cost savings to administrate SC rituximab, considering that almost no patient has a BSA below 1,34 m^2 (see in table 9).

Table 9: Difference between IV and SC formulation and cost savings, according to the BSA. No discount on the IV form and 15% discount on the SC form			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	31,33	192,13	/
1,61 -1,86	2 414,29	2 575,09	/
1,87 -2,13	4 797,25	4 958,05	/
2,14 -2,40	7 180,21	7 341,01	/

4.3.5.2. 10% discount on the IV form and 15% on the SC form

Considering 10% and 15% discount on the IV and SC formulations respectively, it was cost saving to administrate IV rituximab to patients with a BSA ≤ 1,60 m^2 (see in table 10). Above this value, that was SC rituximab which was cost saving.

Table 10: Difference between IV and SC formulation and cost savings, according to the BSA. 10% discount on the IV form and 15% discount on the SC form			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	-1 398,45	/	1 237,65
1,61 - 1,86	746,21	907,01	/
1,87 - 2,13	2 890,88	3 051,68	/
2,14 - 2,40	5 035,54	5 196,34	/

4.3.5.3. 20% discount on the IV form and 15% on the SC form

Considering there were a 20% discount on the IV form and a 15% discount on the SC form, it was cost saving to administrate IV rituximab to patients with a BSA ≤ 1,86 m^2 (see table 11). Above this value, that was SC rituximab which was cost saving.

Table 11: Difference between IV and SC formulation and cost savings, according to the BSA. 20% discount on the IV form and 15% discount on the SC form			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	-2 828,23	/	2 667,43
1,61 - 1,86	-921,86	/	761,06
1,87 - 2,13	984,51	1 145,31	/
2,14 - 2,40	2 890,88	3 051,68	/

4.3.5.4. 30% discount on the IV form and 15% on the SC form

Considering there were a 30% discount on the IV form and a 15% discount on the SC form, it was cost saving to administrate IV rituximab to patients with a BSA ≤ 2,13 m^2 (see table 12). Above this value, that was SC rituximab which was cost saving.

Table 12: Difference between IV and SC formulation and cost savings, according to the BSA. 30% discount on the IV form and 15% discount on the SC form			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 -1,60	-4 258,00	/	4 097,20
1,61 -1,86	-2 589,93	/	2 429,13
1,87 -2,13	-921,86	/	761,06
2,14 -2,40	746,21	907,01	/

4.3.5.5. 40% discount on the IV form and 15% on the SC form

When there were a 40% discount and a 15% discount on the IV and SC formulation respectively, it was always cost saving to administrate IV rituximab considering that almost no patient has a BSA above 2,40 m^2 (see table 13).

Table 13: Difference between IV and SC formulation and cost savings, according to the BSA. 40% discount on the IV form and 15% discount on the SC form			
BSA (m^2)	Difference IV – SC (€)	Cost savings with SC rituximab (€)	Cost savings with IV rituximab (€)
1,34 - 1,60	-5 687,78	/	5 526,98
1,61 -1,86	-4 258,00	/	4 097,20
1,87 -2,13	-2 828,23	/	2 667,43
2,14 -2,40	-1 398,45	/	1 237,65

4.3.6. Summary of the results

The next section presents a summary of the results previously obtained. First, saving through each type of administration were presented. Then the application to routine medical practice was made.

4.3.6.1. Savings through each type of administration

Savings through each type of administration were summarized in the next section. First, only IV discounts were considered. Then, both IV and SC discounts were considered.

4.3.6.1.1. With only IV discount

It was cost saving to use the IV form up to a maximum BSA of 1.60 m^2, 1,86 m^2, 2.13 m^2, and 2.40m^2 with IV discounts of 0%, 10%, 20%, and 30% respectively (see in table 14).

Table 14: BSA value below which IV use is cost savings and above which SC use is cost savings, depending on discount.

Discount on the IV form	Discount on the SC form	Savings through IV use	Savings through SC use
0%	0%	≤ 1.60 m^2	> 1.60 m^2
10%	0%	≤ 1.86 m^2	> 1.86 m^2
20%	0%	≤ 2.13 m^2	> 2.13 m^2
30%	0%	≤ 2.40 m^2	> 2.40 m^2

4.3.6.1.2. With IV and SC discounts

It was cost saving to use the IV form up to a maximum BSA of 1.33 m^2, 1.60 m^2, 1.86m^2 and 2.13 m^2, 2.40 m^2 and 2,94 m^2 with IV discounts of 0%, 10%, 20%, 30%, and 40% and SC discount of 15% (see in table 15).

Table 15: BSA value below which IV use is cost savings and above which SC use is cost savings, depending on discount.

Discount on the IV form	Discount on the SC form	Savings through IV use	Savings through SC use
0%	15%	≤ 1.33 m^2	> 1.33 m^2
10%	15%	≤ 1.60 m^2	> 1.60 m^2
20%	15%	≤ 1.86 m^2	> 1.86 m^2
30%	15%	≤ 2.13 m^2	> 2.13 m^2
40%	15%	≤ 2.40 m^2	> 2.40 m^2

4.3.6.2. Application to routine medical practice

The results found so far showed a tipping point BSA below which it was cost saving to administrate IV rituximab and above which it was more interesting to administrate SC rituximab. Nonetheless, as mentioned before, in routine medical practice, all the patients receive the same formulation, either SC or IV. The hospital buys one formulation or the other, not both.

In order to conclude on the formulation which had to be used in practice, the tipping point related to each discount was compared to the mean BSA. Then the decision rule was applied, namely:

- If the tipping point was below the mean BSA → SC formulation was cost savings.
- If the tipping point was above the mean BSA → IV formulation was cost savings.

4.3.6.2.1. Comparison with mean BSA of Belgians affected by MCL

In routine medical practice, if there was no discount, the SC formulation was cost saving. It was also the case when only a 10% discount was proposed on the IV formulation. From a 20% discount on the IV form (and still no discount on the SC form), IV rituximab was cost saving (see table 16).

When a discount of 15% was applied on the SC rituximab, SC rituximab was cost saving, in routine medical practice, up to a proposed discount of 20% on the IV form. Beyond this percentage (and with still 15% discount proposed on the SC form), IV rituximab was cost saving (see table 16).

Table 16: Comparison between the BSA tipping point and the mean BSA of Belgium to identify the administration route, which is cost saving, depending on the discount.

Discount on the IV form	Discount on the SC form	Tipping point (m^2)	Mean BSA of Belgians (m^2)	Cost savings administration route
0%	0%	1,60	1,92	SC
10%	0%	1,86	1,92	SC
20%	0%	2,13	1,92	IV
30%	0%	2,40	1,92	IV
0%	15%	1,33	1,92	SC
10%	15%	1,60	1,92	SC
20%	15%	1,86	1,92	SC
30%	15%	2,13	1,92	IV
40%	15%	2,40	1,92	IV

4.4. Patient time

At the CHU UCL Namur, the time of arrival of each patient was registered. The time of initiation of rituximab administration was also registered. In order to evaluate the total hospital stay, infusion times according to the SmPC were added to the time spent by the patient in the hospital between his arrival and the initiation of rituximab administration. Thus, the theoretical administration times were added. For IV administration, 90 minutes were added and for SC administration, 5 minutes administration and 15 minutes observation time were added.

This evaluation was available for 48 IV and 50 SC administrations. The mean duration of hospital stay for IV rituximab was 3h15 (3h15±0h38) versus 2h12 (2h12±1h13) in the SC group. Meaning that patient time in the hospital was reduced by 32,3% with SC rituximab. These times spent in the hospital were longer than the theoretical administration times. Meaning also that a part of the time spent in the hospital was dedicated to other activities.

When administration times were removed, the time spent in the hospital (thus, before the administration) were 1h45 (3h15-1h30) in the IV group and 1h52 (2h12-0h20) in the SC group. This time was dedicated to other concerns such as making a blood test, waiting for the results, waiting to see the doctor, going to see the doctor, waiting for medication, … This time before administration was approximately the same in both groups. It represented the most part of the time spent in the hospital in both groups.

Equivalence of variances between mean time spent in the hospital in each group was tested. The equivalence of the variances was rejected. Then, a student test to compare the mean time spent in the hospital in both groups could not have been performed.

5. Discussion and conclusion

5.1. Discussion

5.1.1. Patient population

The clinical characteristic which was at the center of the analysis is the BSA. What was interesting is that the mean BSA of the 13 patients was the same as the calculated mean BSA of Belgians affected by MCL. Thus, even if the CHU-UCL Namur population was too small to draw conclusions on the mean BSA of Belgians affected by MCL, the calculated mean BSA confirmed this value. The results and the conclusion of the study on the formulation to use in routine medical practice were, therefore, the same for Belgians in general and for the CHU-UCL Namur population.
The calculation of the mean BSA of Belgians affected by MCL was based on the calculated percentage of men affected with MCL. This was based on the fact that men are 2 to 3 times more affected than women. This calculated percentage was equal to 70,84%, which was approximatively the same percentage as the percentage of men affected in the 13 patients; in the CHU-UCL Namur population, men represented 69,23% of patients affected by MCL. The fact both means of BSA were equivalent and both percentages of men affected were equivalent, gave the information that, even if the population the CHU-UCL Namur population was small, it represented fairly well the Belgians population affected with MCL.

The median age at diagnosis was 69 in comparison with 60 to 70 years like said in the literature. The stage of the disease at diagnosis was mainly stage III or IV, confirming what was said in the literature.

What could be surprising was that performance status during maintenance therapy was higher than at diagnosis. It was because, during maintenance therapy, patients were affected by the side effects of the therapy. Thus, the performance status decreased. Therefore, the fact performance status decreased during the therapy could seem logical.
Concerning performance status during therapy, a difference between both groups had to be noticed. Approximately 10% of the collected performance status were ≥ 2. In the IV group, only one out of the 36 data collected was ≥ 2, whereas, in the SC group, 7 out of the 37 data collected were ≥ 2. This could be explained by the fact that, in the SC group, patients were older given the fact the SC group was composed of patients included in the MCL-R2 elderly study, which had, as one of the inclusion criteria to be ≥ 60 years. While in the IV group, patients were younger.

Concerning unknown values, there were no more unknown values in one group than in the other. For several criteria, there was only one missing data, related to the patient treated on another site before maintenance therapy. The characteristic for which there were the most unknown values was performance therapy. However, as already mentioned, there was still the same number of data collected in each group (36 in the SC group and 37 in the IV group). Finally, there were 2 and 1 unknown values in the SC and IV group respectively about LDH level during maintenance therapy.
All this suggested that the group in which patients were, did not influence the missing data

5.1.2. Patient time

In the present study, patients spent approximately 32% less time in the hospital in the SC group. Patient times in the hospital were, on average, 3h15 and 2h12 for IV and SC injection

respectively. These times were calculated based on the time between the arrival of the patient in the hospital and the theoretical end of injection (or observation for SC form) time. In the SmPC, recommended administration times (taking into account observation time after SC injection) were 1h30 for an IV injection and 20 min for SC rituximab. The difference in administration time between each formulation was approximately 1 hour, which was approximatively reflected in the calculated time that patients spend in the hospital.

The paper by de Cock et al. described chair times of 4h22 (including 3h infusion) and 1h07 (including 8 min infusion) for IV and SC rituximab. In the IV group, the difference between chair time by de Cock et al. and patient time in the present study was explained by the longer infusion time in the paper by de Cock et al. If infusion times were subtracted, present patient time was equal to 1h45 (3h15 – 1h30) and chair time in the paper by De Cock et al was equal to 1h22 (4h22 – 3h). Meaning that patient time in the hospital outside of infusion time, was 23 min longer than chair time (outside of infusion time) in the paper by de Cock et al. What seemed logical since patient time in the hospital is equal to chair time plus some waiting time [24].
In the SC group, the difference between chair time by de Cock et al. and patient time in the present study was more surprising. When infusion times were subtracted and remaining times compared, chair time without infusion time in the paper by de Cock et al. was approximatively equal to 1h and patient time in the present study without infusion time was equal to 2h07. This could be explained by the fact hospitals in different countries did not follow the same routine clinical practices. Therefore, the processes and the times were different. Some hospitals could have already worked on improving the process related to SC administration, to decrease patient time in the hospital. While other hospitals followed the same clinical practices whatever the formulation administrated, apart from the administration itself.

Knowing the infusion times and looking at patient time spent in the hospital (2h12 and 3h15), it was interesting to notice that a big part of the time spent in the hospital was not related to the injection of the rituximab itself. Here, patients spent 1h52 (2h12-0h20) and 1h45 (3h15-1h30) in average at hospital before receiving SC or IV rituximab. The patient spent a lot of time on other concerns like doing a blood test, waiting for the results, waiting to see the doctor, going to see the doctor, waiting for medication, …. The time before rituximab administration was approximatively the same in both groups. Meaning the time for other concerns before the rituximab administration was not impacted by the further way of administration. Nevertheless, this time could seem longer to patients receiving SC rituximab. When patients receive the SC formulation, which constitutes a big time saving related to a shorter administration time, they expect to be treated faster before receiving rituximab injection. However, that is not the case. As said in the paper by Fargier et al., in order "to improve patient care, SC formulations have to be associated to a change in the organization of care", in order to decrease the waiting time for the patient before injection [27].
Improving the time apart from the administration time, in the case of an SC administration could decrease again the time spent in the hospital; enabling a faster workflow and enabling patients to take greater benefit from the fact that their formulation is administered in a much shorter time.

5.1.3. BIA

5.1.3.1. Data related to time

Nurses' time was controversial as already mentioned. Some papers reported a longer nurses' time with IV rituximab, which made sense since the administration time was longer. Nurses' times reported were 23,7min vs 11,8min for IV and SC rituximab in the SMABcare study. The paper by de Cock et al. reported ranges of nurse time: 12,2 to 40 min and 7,8 to 19,9 min for

IV and SC rituximab respectively. The differences originated from different clinical practices and thus, different process flows, taking more or less time [24,27].
On the contrary, other papers reported a longer nurse time with SC rituximab like the paper by Mihajlovic et al. where nurses' times were equal to 13,65 and 16,50 min for IV and SC rituximab. The longer involvement of nurse with SC rituximab, despite the shorter administration time was justified by the fact that "an SC injection requires active nurse time during the entire administration time, whereas an IV infusion only requires time for connecting and switching infusion bags and checking the infusion pump" as said in the paper by Mihajlovic et al. In CHU-UCL Namur, nurses agreed with the argument advanced by the paper by Mihajlovic et al. The time required to connect, switch infusion bags and check the infusion pump, was shorter than the active nurses' time required in a SC administration [25].
Given that nurse time could not have been evaluated in the present study, the times included in the BIA were those by Mihajlovic et al. Nevertheless, it should be interesting to analyze precisely nurses' time in a further study to have data to confirm that nurses' time was longer for an SC injection.

Administration times in the present study were 90 min vs 20 min (5 min infusion + 15 min observation). In papers, it varied from 5 to 8 min infusion with SC rituximab and from 90 min to 180 min with IV rituximab. Anyway, the administration time was much shorter in the case of an SC administration. The differences between infusion times were explained by the fact routine medical practices were different according to the country. In addition, infusion time is different on whether this is the first-time rituximab is administered or not. During the first administration, the pace of infusion is slower, and the administration goes up to 180 min. While during the next administration, the pace of infusion is faster. In the present study, we weren't in the case of a first injection since patients had all previously had rituximab administered during the first phase of their treatment. The recommended administration times in the SmPC are those for the next infusions [24,25].
Moreover, inside a country, not all hospitals strictly followed the recommendations. With experience and practice, each hospital acquires its "own recommended administration time". If it is possible to faster the process without compromising safety, rituximab is administered faster. Even in CHU-UCL Namur, the practical administration times aren't the same as those recommended in the notice. Because processes are different according to the site, times were also different. In the present study, theoretical administration times were taken into account in order to avoid the bias linked to encoding inaccuracies. In addition, as said, practical administration times are different according to the site.

It was said that nurses had to stay next to the patient during all the administration time, including observation time. Then, nurse time should be equal to 20 min. However, nurse involvement used for a SC administration was 16,50 min. This time came from the Nederlands but, in that country, the recommended administration times are the same as those in Belgium, so, 20 min for a SC administration. The difference originated from the fact that hospitals do not strictly follow the recommendations. The nurse may not stay next to the patient during the last minutes of the observation time. Or maybe the observation time in routine medical practice is shortened[25].

Concerning drug preparation time, it also varied since it also depends on the routine medical practice of the hospital. In the paper by Mihajlovic et al. drug preparation times were 242,57 and 226,50 seconds for IV and SC rituximab. In the SMABcare study, they were 546 and 210 seconds for IV and SC rituximab. Here, drug preparation times were 294 and 0 seconds for IV and SC rituximab. In the routine medical practice of CHU-UCL Namur, SC rituximab was not

prepared in advance because it did not require any preparation time since it is the nurse who has to extract and then directly inject the drug [25,27].
In spite of the variations that can be found depending on routine clinical practices of each site, in every case, pharmacist time was longer with the IV formulation.

5.1.3.2. Data related to cost

In the present study, the nursing cost was about 4,33 and 5,23€ for IV and SC administration. This was an estimated cost based on the nursing time in the paper by Mihajlovic et al. and on salary cost in the CHU-UCL Namur. As said above, performing a further prospective study could enable to calculate exact nursing time and thus, could enable to have the exact nurse cost. In the literature, other nursing costs were found, mainly due to the variations in nurses' times and also due to small variations in salary costs.

Concerning pharmacist salary cost, whether in the literature or in the present study, the cost was higher when the injection was IV. In CHU-UCL Namur, the costs were 2,45€ and 0€. In the literature, the costs were 9,30€ vs 3,60€ in the SMABcare study (for 2 technicians). In the paper by Mihajlovic et al, the salary costs of pharmacists were 2,89€ vs 2,70€. The difference originated from different practices, so different preparation times and thus, different salary costs. Salary cost per hour depends also on the seniority and was also different depending on the country. Also, it was different depending on whether it was a pharmacist or an assistant who prepared the drug. Also, in some hospitals, for example, two pharmacists are involved: one prepares the drug while the other supervises the process. Also, in some centers, the way of administrating the IV rituximab was different (through an implantable port or a peripheral vein)[25,27].
In the present study, the salary costs were calculated based on the fact that was a pharmacist and not an assistant who prepared the drug. Nevertheless, if that had been an assistant who prepared, the costs would have been equal to 1,32€ for IV rituximab and still 0€ for IV rituximab. This small difference would have made no difference to the results given the high cost of the drugs and therefore the almost trivial cost that represented this salary cost.

About material cost, it was always higher with IV rituximab. In the present study, material costs were 16,86€ and 5,01€ for IV and SC injections. A significant difference between both formulations had already been found in the paper by Mihajlovic et al. (5,40€ vs 1,38€) and in the SMABcare study (11,0€ vs 0,51€). Again, the differences between all those costs originated from the different routine clinical practices. Also, cost differences between countries influenced[25,27].

Concerning patient chair time cost, when the perspective of the hospital was taken into account, this cost could be reflected by day care treatment cost, which was collected. In the paper by Mihajlovic et al, day care treatment cost depended on the time spent in the hospital and thus, on the formulation. The costs were 76,55€ and 184,48€ for SC and IV rituximab. In the present study, the day care treatment cost was the same for all patients, regardless of the time spent during the day. There were no differences in terms of costs related to patient chair time; it was 126,20€ whatever the formulation. However, it makes sense that if patients spend more time in the hospital, the latter can care for fewer patients a day, which represents a cost for the hospital. But a question arises; even if patients spend less time in the hospital and therefore if the hospital is able to welcome more patients, these patients must "exist". In big hospitals, decreasing chair time could impact the cost by enabling to increase in the number of sessions. It could increase annual earnings. But in small hospitals, even if the chair time decrease, enabling to care more patients, the additional patients to care does not exist. There are no additional patients.

Nurse salary cost, pharmacist salary cost, material cost, and day care treatment cost are additional non-drug costs, related to the administration of rituximab. The difference of additional non-drug costs between each formulation was 13,40€ for one single administration. This difference was small, almost marginal, in comparison to the drugs costs equal to 1398,67€ or 1586,64€ for SC and IV rituximab, for a patient with a mean BSA (1,92 m^2). For a patient with this BSA, this additional cost represented approximatively 1% and 0,85% of the cost of one injection of SC and IV rituximab respectively. What represented a trivial cost in comparison with the drugs costs.

5.1.3.3. Price calculation without discount

When there was no discount applied, it was less expensive to administrate the IV formulation up to patients with a BSA smaller or equal to 1,60 m^2. Above this value, SC rituximab should be preferred in order to save cost.
In routine medical practice, all patients receive the same formulation. Thus, given that the mean BSA of Belgians affected by MCL is 1,92 m^2, it was always cost saving to administrate the SC formulation, when no discount was applied, neither on IV nor on SC rituximab.

5.1.3.4. Price calculation with IV discount

With a 10% discount, the tipping point raised to 1,86 m^2. Below this value, SC rituximab should be preferred in order to save cost. In routine medical practice, all patients receive the same formulation. Thus, given that the mean BSA of Belgians affected by MCL was 1,92 m^2, SC formulation should still be used.
With a 20 % discount, the tipping point changed to 2,13 m^2. Below this value, IV rituximab was cost-saving and above this value, the SC formulation was cost-saving. Meaning that, when the tipping point was compared to 1,92 m^2, IV rituximab was more interesting in a cost-minimization way in routine medical practice.

From this point, the more the IV discount increased, the more costs were saved by administrating the IV formulation in routine medical practice.

5.1.3.5. Price calculation with IV and SC discount

So far, only IV reduction had been discussed, but a small reduction of up to 15% could also be applied on the SC form. As said before, the discounts are reduction proposals that the firm makes to the hospital. Then, when it will be mentioned that there is a discount of 10% on the IV form and a discount of 15% on the SC formulation, it is hypothetical. The hospital doesn't really get both discounts since it orders only one formulation. The hospital only buys the most advantageous formulation, for itself, according to the discounts proposed to it.

When there was a 15% discount proposed on the SC form and 0% on the IV formulation, SC rituximab was always cost saving. Patient BSA should be smaller or equal to 1,34 m^2, which is very rare, in order to make IV use more advantageous. Consequently, in routine medical practice SC formulation was the best one since the mean BSA of Belgians affected by MCL was higher than the tipping point.

The mean BSA of Belgians affected by MCL was also higher than the tipping points (1,60 m^2 and 1,86 m^2) when there were a 15% discount on the SC formulation and 10% or 20% on the IV formulation. In these cases, SC rituximab should be the formulation of choice in routine medical practice.

From a 30% discount on the IV formulation (with still a 15% discount on the SC form), the tipping point below which the IV formulation should be preferred and above which the SC formulation was better, increased beyond mean BSA of Belgians affected by MCL. Meaning that, in routine medical practice, the IV formulation was the most advantageous when those discounts were proposed. From that, the more the IV discount increased, the greater the benefit was.

5.2. Limitations

This study presented some bias. The first one concerned patient inclusion. The study was performed on the site of Yvoir of the CHU-UCL Namur and, since the disease is rare, only 16 patients were treated for MCL in this site from March 2015 until September 2020. Then, all the patients possible to enroll in the study were enrolled, without any sample size calculation. In addition, a selection bias exists, since the study was performed without any randomization.

Moreover, the present study was based on a lot of times previously collected and reported in a database. It is important to stay aware that a difference in data report accuracy could exist between the IV group and the SC group. Given that IV data were collected according to routine medical practice, this data collection may have been subject to less rigor than the data collected for the SC arm, as part of a clinical trial.
In addition, the data source varied according to the data. Some were specific to the CHU-UCL Namur, others originated from the paper by Mihajlovic et al. Some were the same for all hospitals in Belgium like ex-factory drug costs whereas it was not the case for others. The BIA was performed with the aim of being able to extend the results. Nevertheless, the generalization of the results to other sites should be performed with caution, and data sources have to be checked in order to know if the input variables are the same for the specific site for which the results will be generalized.

In addition, nothing was said about potential drug spillage during IV drug preparation. Given the high cost of rituximab, spillage and waste could have an important impact.

Another limitation already mentioned is the fact that the proportion of patients affected with MCL in Belgium is a theoretical calculated proportion and not a “real” proportion based on a big sample. Also, the men BSA of Belgians affected with MCL was a calculated mean. Thus, those data were approximations.

Concerning patient time, theoretical administration time was taken into account to reduce the bias related to late time encoding. However, this theoretical time was not the real one, it could less reflect the reality. In addition, the arrival time of patients in the hospital was taken into account in the study. As already said, this time was correct since the data encoding of the arrival of the patient is always accurate. Nonetheless, all patients did not arrive in the hospital right at the time of their appointment. Some patients arrive in advance, others arrive right on time while others are late. That could skew the results. Particularly if patients tend to arrive earlier, or right on time, or late, for a type of administration and not for the other (due to the age of the patient or to the way of administrating the drug itself). Moreover, a statistically significant difference between patient time in the hospital in both groups could not have been proven since variances of both groups were not equivalent. Then, a student test comparing both means could not have been performed.

5.3. Perspectives

The present study took the perspective of the hospital. It could be interesting to repeat this kind of study and then look at the perspective of the society, by investigating societal costs like loss of productivity at work, informal cares, traveling expenses, …

Another point is patient preference. A prospective analysis could explore this point on a big and randomized population. That could enable to confirm the trends towards the preference for SC formulation or not. Moreover, patient satisfaction which is still controversial could be investigated further. In addition, HRQoL could also be examined, focusing exclusively on patients affected by MCL. HRQoL has already been evaluated on a population of patients with FL but focusing further on patients affected with MCL could be interesting. Even if MCL and FL are both cancers affecting B-cells, they are still different and may have some particularities affecting HRQoL in a different way.

In addition, performing the same BIA prospectively on a bigger population, in several countries could enable to collect exact patient times, nurse times, pharmacist times. That could be interesting in order to get more accurate results and applicable to a large number of countries.

5.4. Conclusion

Even if there were several non-drug costs associated with the administration of rituximab, those costs represented a very small part of the budget involved in the maintenance therapy of MCL. The costs involved in rituximab administration varied a lot, due to the BSA of the patient and due to discount, that could be proposed. Then, there was not a formulation that was always more interesting, economically speaking, in routine medical practice.

IV rituximab was found cost saving in routine medical practice in most situations. SC formulation was cost saving in only three situations: 1) with no discounts, 2) with only 10% IV discount and 3) when there were 15% SC discount and 20% or less discount on the IV form. In any other case, IV rituximab should be preferred.

About patient time in the hospital, it was roughly 1 hour longer with IV formulation, due to the longer infusion time. Nevertheless, administration time did not represent the most part of the time spent by patients in the hospital. In the future, the process could be improved in order to decrease the time before the administration of rituximab.

6. Bibliography

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Annex 1

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- Does increased use of generic medicines by elders in Belgium help to contain escalating health care budgets? *Journal of Aging & Social Policy*, *26* (3), 266-280 (2014).
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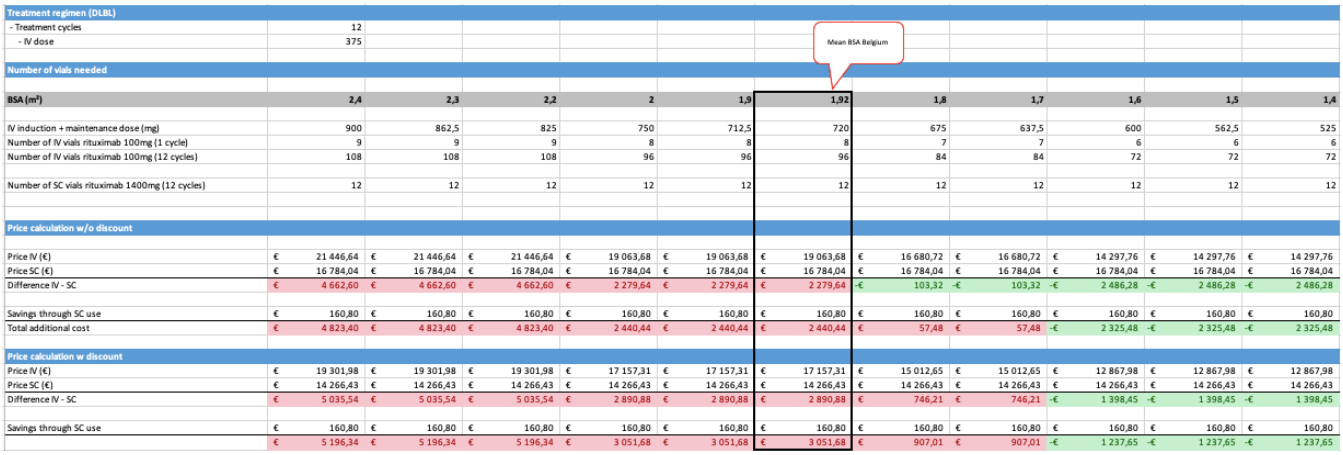
Annex 2

Additional cost SC vs. IV					
Input 1: time estimate the Netherlands, labor cost estimate Belgium					(Mihajlović, 2017 & Tjalma, 2018)
		IV		**SC**	
Mean nursing time	€	4,33	€	5,23	
Mean pharmacy preparation time	€	2,45	€	-	
Mean time spent in chemotherapy unit	€	126,20	€	126,20	
Material costs	€	16,86	€	5,01	
Total	**€**	**149,84**	**€**	**136,44**	
Additional cost IV per administration	€	13,40			
Additional cost IV per maintenance therapy (12 cycles)	€	160,80			

First sheet of the economic model. Mean time spent in chemotherapy unit is the day care treatment cost.



Treatment regimen (DLBL)												
- Treatment cycles	12											
- IV dose	375											
							Mean BSA Belgium					
Number of vials needed												
BSA (m²)	**2,4**	**2,3**	**2,2**	**2**	**1,9**	**1,92**	**1,8**	**1,7**	**1,6**	**1,5**	**1,4**
IV induction + maintenance dose (mg)	900	862,5	825	750	712,5	720	675	637,5	600	562,5	525
Number of IV vials rituximab 100mg (1 cycle)	9	9	9	8	8	8	7	7	6	6	6
Number of IV vials rituximab 100mg (12 cycles)	108	108	108	96	96	96	84	84	72	72	72
Number of SC vials rituximab 1400mg (12 cycles)	12	12	12	12	12	12	12	12	12	12	12
Price calculation w/o discount											
Price IV (€)	€ 21 446,64	€ 21 446,64	€ 21 446,64	€ 19 063,68	€ 19 063,68	€ 19 063,68	€ 16 680,72	€ 16 680,72	€ 14 297,76	€ 14 297,76	€ 14 297,76
Price SC (€)	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04	€ 16 784,04
Difference IV - SC	€ 4 662,60	€ 4 662,60	€ 4 662,60	€ 2 279,64	€ 2 279,64	€ 2 279,64	-€ 103,32	-€ 103,32	-€ 2 486,28	-€ 2 486,28	-€ 2 486,28
Savings through SC use	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80
Total additional cost	€ 4 823,40	€ 4 823,40	€ 4 823,40	€ 2 440,44	€ 2 440,44	€ 2 440,44	€ 57,48	€ 57,48	-€ 2 325,48	-€ 2 325,48	-€ 2 325,48
Price calculation w discount											
Price IV (€)	€ 19 301,98	€ 19 301,98	€ 19 301,98	€ 17 157,31	€ 17 157,31	€ 17 157,31	€ 15 012,65	€ 15 012,65	€ 12 867,98	€ 12 867,98	€ 12 867,98
Price SC (€)	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43	€ 14 266,43
Difference IV - SC	€ 5 035,54	€ 5 035,54	€ 5 035,54	€ 2 890,88	€ 2 890,88	€ 2 890,88	€ 746,21	€ 746,21	-€ 1 398,45	-€ 1 398,45	-€ 1 398,45
Savings through SC use	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80	€ 160,80
	€ 5 196,34	€ 5 196,34	€ 5 196,34	€ 3 051,68	€ 3 051,68	€ 3 051,68	€ 907,01	€ 907,01	-€ 1 237,65	-€ 1 237,65	-€ 1 237,65

Second sheet on the economic model. The cost with discount was calculated with a discount of 10% on the IV form and a discount of 15% on the SC form.

Annex 3

Table 1: Description of all the materials (and their cost) needed for both injections			
IV rituximab		**SC rituximab**	
Tevadaptor luer-lock connector	0,77€	Tevadaptor luer-lock connector	0,77€
Tevadaptor seringue connector	4,06€	Tevadaptor seringue connector	4,06€
Tedaptor vial adaptator x2	7,26€	Syringe LL 20 mL	0,13€
Syringe 50ml	0,22€	Bouchon combi	0,04€
0.9% NaCl infusion 250ml	1,26€	Injection needle	0,013€
Infusion line VLON 10	3,29€		
Total material cost: 16,86€		**Total material cost: 5,01€**	