Variation in tumour necrosis factor-alpha inhibitors usage for Rheumatoid Arthritis between Portugal and The Netherlands

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Abstract

Objective: Analyse the evolution of biological tumour necrosis factor alpha (TNFalpha) inhibitors utilisation in the treatment of rheumatoid arthritis (RA) and identify the reasons for the observed variation.

Methods: Two western European countries were selected for this analysis, Portugal and the Netherlands. Country characteristics, treatment guidelines and RA prevalence were obtained from the literature. Patient characteristics were obtained from the literature and from the data made available by the University Medical Center Utrecht, for Portugal and the Netherlands, respectively. Annual utilisation rates of TNFalpha inhibitors between 2008 and 2013 were expressed as defined daily doses (DDDs)/1000 inhabitants/day.

Results: TNFalpha inhibitors utilisation varied from 0.18, in 2008, to 0.46 DDDs/1000 inhabitants/day, in 2013, in Portugal and from 0.98, in 2008, to 1.64 DDDs/1000 inhabitants/day, in 2013, in the Netherlands. Clinical guidelines, variations in GDP per capita, total health expenditure, medical goods expenditure and drug distribution channel, appear to have had limited impact on TNFalpha inhibitors utilisation. On average, Dutch RA patients under therapy with TNFalpha inhibitors appear to younger than their Portuguese counterparts.

Conclusions: TNFalpha inhibitors utilisation continues to be increasing, despite the negative influences caused by the economic recession and posterior austerity measures. This increase in TNFalpha inhibitors utilisation was not equal in Portugal and in the Netherlands, which lead to a bigger difference in utilisation between both countries. The high percentage of undiagnosed Portuguese rheumatic patients might be one of the leading reasons for the anaemic utilization of TNFalpha inhibitors. The number of rheumatologists per 100,000 inhabitants, improved clinical efficiency and a reduction in drug pricing all seem to have positively influenced utilisation.

Keywords: Biologicals, TNFalpha inhibitors, utilisation, rheumatoid arthritis.

Resumo

Objetivo: Analisar a utilização dos biológicos inibidores do fator de necrose tumoral alfa (TNF-alfa) no tratamento de artrite reumatoide (AR) e identificar as razões para a variação de utilização observada.

Metodologia: Dois países europeus ocidentais foram selecionados para esta analise, Portugal e a Holanda. As características dos países, guidelines de tratamento e a prevalência foram obtidos da literatura. As características dos doentes com AR foram obtidas da literatura e a partir dos dados disponibilizados pelo *University Medical Center Utrecht*, para Portugal e Holanda, respetivamente. Ratios de utilização anuais dos inibidores do TNF-alfa entre 2008 e 2013 foram demonstrados como Dose Definida Diária (DDD)/1000 habitantes/dia.

Resultados: A utilização dos inibidores do TNF-alfa variaram de 0.18, em 2008, para 0.46 DDD/habitantes/dia, em 2013, em Portugal e de 0.98, em 2008, para 1.64 DDD/habitantes/dia, em 2013, na Holanda. Guidelines clinicas, variações no GDP per capita, despesa total em saúde, despesa com produtos de saúde e canal de distribuição dos medicamentos, parecem ter tido um impacto limitado na utilização dos inibidores do TNF-alfa. Doentes holandeses com artrite reumatóide sob terapia dos inibidores do TNF-alfa são, em média, mais novos que os seus contrapartes portugueses.

Conclusão: A utilização de inibidores do TNF-alfa continua a aumentar, mesmo com os efeitos negativos causados pela recessão económica e das medidas de austeridade implementas posteriormente. O aumento de utilização de inibidores do TNF-alfa não foi igual em Portugal e na Holanda, levando assim a um aumento na diferença de utilização destes medicamentos entre os dois países. A elevada percentagem de doentes portugueses não-diagnosticados pode ser uma das principais razões por detrás da utilização anémica de inibidores do TNF-alfa. O número de reumatologistas por 100.000 habitantes, aumento da eficiência clinica e reduções no preço dos fármacos parecem todos ser fatores que influenciaram positivamente a utilização destes fármacos.

Palavras-chave: Biológicos inibidores do fator de necrose tumoral alfa, utilização, artrite reumatóide

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Acronyms

ACPA - Anti-Citrullinated Protein Antibody

ACR - American College of Rheumatology

ATC - Anatomical Therapeutic Chemical Code

bDMARDs - Biological Disease-Modifying Antirheumatic Drugs

boDMARDs - Biological Originator Disease-Modifying Antirheumatic Drugs

bsDMARDs - Biosimilar Disease-Modifying Antirheumatic Drugs

CBO - Kwaliteitsinstituut voor de Gezondheidszorg CBO

CHNM - Código Hospital Nacional do Medicamento

csDMARDs - Conventional Synthetic Disease-Modifying Antirheumatic Drugs

DALY's - Disability-Adjusted Life Years

DAS28 - Disease Activity Score based on 28 joint counts

DDD - Defined Daily Dose

DMARDs - Disease-Modifying Antirheumatic Drugs

DRS - Drugs Remuneration System

DTCs - Diagnosis Treatment Combinations

EC - European Commission

ECB - European Central Bank

EMA - European Medicines Agency

EULAR - European League Against Rheumatism

EU - European Union

GCs - Glucocorticoids

GDP - Gross Domestic Product

HAQ - Health Assessment Questionnaire

ICERs – Incremental Cost-Effectiveness Ratio

IL - Interleukin

IMF - International Monetary Fund

MTX - Methotrexate

NVR - Nederlandse Vereniging voor Reumatologie

PAB - Patient access to biologics

QALYS - Quality-Adjusted Life Years

RA - Rheumatoid Arthritis

Reuma.pt - Registo Nacional de Doentes Reumáticos

RF – Rheumatoid Factor

RHA - Regional Health Administration

RMDs - Rheumatic and Musculoskeletal Diseases

sDMARDs - Synthetic Disease-Modifying Antirheumatic Drugs

SPR - Portuguese Society of Rheumatology

TNFalpha - Tumour Necrosis Factor-alpha

tsDMARDs - Targeted Synthetic Disease-Modifying Antirheumatic Drugs

VHI - Voluntary Health Insurance

WTP - Willingness to Pay

ZIN - Zorginstituut Nederland

1. Introduction

The Universal Declaration of Human Rights states that “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control”(1). This is a common commitment of all western European democracies, however, making this dream a reality seems as difficult as it was in 1948. It is undeniable that there have been many improvements over since the last century, human life expectancy, for example, has improved at a rate of more than 3 years per decade since 1950, with the only exception being the 90’s decade(2). But as people age, more comorbidities start to develop, driving the need for more and better medical care. The result of this ever-increasing need for healthcare is clear, according to Eurostat, the average healthcare expenditure relative to Gross Domestic Product (GDP) in the European Union (EU) in 2013 was around 9.4% and the fact that new and more effective medication is becoming available seems to question the ideal of equal drug accessibility for all citizens. Biologics such as Tumour Necrosis Factor alpha (TNFalpha) inhibitors are now part of the therapeutical arsenal against Rheumatoid Arthritis (RA), but the costs associated with these drugs force many policymakers to impose certain limitations on their clinical application, effectively limiting their widespread use. This type of decisions is certainly not new and don’t apply only to these specific drugs, in fact, they have become an unwanted but required widespread phenomenon.

Drug utilization inequality between countries, a direct consequence of these restrictions, has been widely studied, particularly in the case of TNFalpha inhibitors and it seems to be somewhat correlated to a number of factors such as GDP, expenditure on health, access and availability of care, global drug prices and clinical guidelines(3–7). Portugal and the Netherlands are two European countries with significant differences in these factors, which might explain the different utilisation of TNFalpha inhibitors, in defined daily dose (DDD)/1000 inhabitants/day, noted in past studies(5). But this paradigm might have slightly shifted since 2008, when both countries, while under an economic recession, were required to reduce their healthcare expenditure, while still maintaining adequate access to new and expensive drugs. One of the solutions for the increasing prices of innovative drugs has been to centralise the distribution pathway in the hospital sector, effectively increasing their bargaining power in hopes of driving down prices and increasing sustainability. This system, when compared to the retail distribution channel, has the disadvantage of being a more controlled process due to the hospital’s budgetary constraints and the long and complicated procedures required to take to

authorise certain medical prescriptions. Despite these limitations, it has become the model of many European countries, including the Netherlands that since 2012 transferred many drugs, including TNFalpha inhibitors, from the retail to the hospital distribution channel. Portugal which has functioned with this model before the financial crisis has also enacted some policy measures to limit hospital expenditure, as for example the 2010 dispatch which forced hospitals in the following years to only acquired medication with a price 7,5% inferior to that practised in 2010(8). It isn't clear how these policies have affected drug utilization, but they serve as a reminder of the precarious situations that policymakers, health professionals and patients are in during this decade. It is easy to argue that RA patients all over Western Europe have now an average quality of life superior to their last century counterparts, but it is still unclear if we be able to adapt to the current challenges and maintain the premises envisioned by the United Nations in 1948. This thesis aims to explore the variation of TNFalpha inhibitors utilization in the treatment of RA as a measure of access to treatment thru a cross-national comparison of Portugal and the Netherlands.

1.1. Rheumatoid Arthritis

1.1.1. Definition and classification criteria for RA

RA is a systemic, autoimmune disease of unknown aetiology that results in chronic inflammation that causes the synovium to thicken, resulting in swelling and pain in and around the joints. If left unchecked, it can lead to cartilage and bone destruction resulting in a joint deformity that cannot be reversed, and thus a large effort has been put into place to guaranty an early diagnosis and aggressive treatment to control RA(9–11). RA is classified as an auto-immune disease, due to the presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), which may precede the clinical manifestation of RA by many years(12,13). This emphasis on early diagnosis has led to a joint effort of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) to review the 1987 RA classification criteria, and thus create the 2010 Rheumatoid Arthritis Classification Criteria which focuses on the detection of the earlier stages of disease that are associated with persistent and/or erosive disease, such as RF and ACPA, rather than defining the disease by its late-stage features, such as radiological changes(14).

Criterion	Score
A. Joint involvement	
1. 1 large joint	0
2. 2-10 large joints	1
3. 1-3 small joints (with or without large joint involvement)	2
4. 4-10 small joints (with or without large joint involvement)	3
5. >10 joints (at least 1 small joint)	5
B. Serology	
1. Negative RF and negative ACPA	0
2. Low-positive RF or low-positive ACPA	2
3. High-positive RF or high-positive ACPA	3
C. Acute-phase reactants	
1. Normal CRP and normal ESR	0
2. Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
1. < 6 weeks	0
2. ≥ 6 weeks	1

Target population: patients who

1. Have at least 1 joint with definite clinical synovitis
2. Patients symptoms and findings cannot be better explained by another disease

Figure 1 - The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. A score of ≥6/10 is needed for classification of a patient as having definite RA. (15)

1.1.2. Prevalence and incidence

It is estimated that the prevalence of RA is approximately 0.5% to 1% of the adult population(16), varying according to the country and region under analyses(16). For example, Southern European countries are estimated to have a lower prevalence than for Northern Europe, while highest rates are found in North America(17,18). Portugal's and The Netherlands RA prevalence was estimated by Kobelt et al as 0.47% and 0.46%(19), respectively, for patients older than 19.

An epidemiological study was recently conducted in Portugal by EpiReumaPt, to produce more data regarding rheumatic and musculoskeletal diseases (RMDs) prevalence. This was an observational and cross-sectional population-based study, with a selected sample of 10.661 individuals, that estimated an RA prevalence of approximately 0.7%(20), a prevalence slightly higher, around 0,2%, than in Kobelt et al(19). This difference in prevalence might be due to a variety of factors, such as a difference in RA diagnostic tolls, changes in demographics and the degree of uncertainty inherently generated by the estimation that Kobelt et al(19) made for many countries, including Portugal.

Despite all of this, Kobelt et al(19) is the only report currently available that allows for a direct comparison of RA prevalence between European countries.

Country	Prevalence > 19 (%)
Denmark	0.58
United Kingdom	0.57
Ireland	0.49
Greece	0.48
France	0.48
Austria	0.47
Portugal	0.47
Netherlands	0.46

Table 1 - Prevalence rates and the estimated number of patients (>19) per Country (adapted). (19)

Women have, in most studies, a higher incidence of RA of around 2:1 to 3:1, when compared to male individuals, suggesting that reproductive and hormonal factors might be influential. There also seems to be a peak in disease onset during the fifth decade of life, as we can observe in annex 1. Smoking habits, infectious agents, ethnicity, genetic, socioeconomic, hormonal and dietary factors, all seem to be related to an increased incidence of RA, but there is still a debate regarding the strength of their influence.(16,21–24)

1.1.3. Mortality and morbidity

Mortality has been positively associated with RA, several studies show an increased mortality in patients with RA when compared with expected rates in the general population(25–27). The standardised mortality for patients with RA ratios varies from 1.28 to 2.9 and there is evidence that these patients have not experienced the same improvement in survival as the general population, resulting in a widening of the mortality gap(27-28). The possible causes of this higher mortality include increased risk from cardiovascular, respiratory, hematologic, gastrointestinal and infectious diseases(27). New treatment options such as methotrexate (MTX) and TNFalpha inhibitors appear to improve patient survival, due to their ability to dramatically reduce disease activity and the development of comorbidities(29,30).

In Europe, there are more than 120 million people affected by RMDs which are considered the number one cause of disability in Europe. These are one of the main causes of absenteeism, work loss and early retirement. In addition, RMDs have a yearly economic burden of more than € 240 billion on public budgets in Europe(31).

Disability-Adjusted Life Years (DALY's), measured according to the gap between current health status and the ideal health situation where the entire population lives, is divided into two inputs, mortality (years of life lost) and disability (years of disability). In RA the greatest share of the disease burden is caused by disability, significantly different from other diseases with a predominant component in mortality, such as cancer and cardiovascular disease, as observed in annex 2(19). Mean utility in RA is low, approximately 0.5, and is showed to rapidly decreases utility from the onset of the disease(19). When patients with RA are compared to the general population, in an age-matched sample, the loss of quality of life varies from 20 to 30%.(19,32)

1.2. Treatment of rheumatoid arthritis

The management of RA rests on several principles. Drug treatment, which comprises disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs and glucocorticoids (GCs), and non-pharmacological measures, such as physical, occupational and psychological therapeutic approaches(33). The agreed standard of care relies mainly on the use DMARDs as the principal option of treatment, since these drugs can reduce or reverse the main signs and symptoms of this disease and thus improve the overall quality of life. DMARDs are divided into two major classes: synthetic and biological, denominated as sDMARDs and bDMARDs, respectively. A new nomenclature proposed in 2013 proposed a new terminology, enabling a greater differentiation between the drugs belonging to each class(34). The conventional sDMARDs (csDMARDs) includes chemical agents such as MTX, sulfasalazine and leflunomide, whereas the subclass targeted sDMARDs (tsDMARDs) includes drugs such as tofacitinib. The bDMARD class is divided two subclasses, the biological originator boDMARDs and the biosimilar DMARD (bsDMARDs)(34).

1.2.1. Biological DMARDs

The need for new and innovative treatment options for diseases led many pharmaceutical companies to engage in the development of biologic drugs, which now account for approximately 27% of the pharmaceutical sales in Europe and have grown at a rate of 5.5% in value sales between 2012 and 2013(35).

For RA this evolution has been evident and is a major consequence of a deeper understanding of the pathophysiological and immunological mechanisms that trigger this disease. bDMARDs have proven to be an effective therapeutically option, either in monotherapy or in combination with a sDMARDs, such as MTX(36). Clear differences in effectiveness between bDMARDs have still not been detected, although there is some evidence of the superiority of tocilizumab 8 mg/kg monotherapy versus adalimumab 40 mg subcutaneous monotherapy group(37).

To date, nine boDMARDs have been approved for the treatment of RA:

- TNFalpha inhibitors - infliximab, etanercept, adalimumab, golimumab and certolizumab pegol;
- Interleukin (IL)-1 blocker – anakinra;
- IL-6 blocker - tocilizumab;
- B-cell depleting agent – rituximab;
- T-cell co-stimulation inhibitor – abatacept.

1.2.2. TNFalpha inhibitors

TNFalpha is a cytokine that plays an important role in joint inflammation. TNFalpha inhibitors target this cytokine, despite their small differences in molecular structure, pharmacodynamics and pharmacokinetics. Presently there are five TNFalpha inhibitors approved in the EU for the treatment of RA, differing from each other due to their molecular structure, approved dosage and administration route, as can be seen in figure 2.

Biologic agent	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab pegol
Molecular structure	Chimeric monoclonal antibody	Soluble TNF receptor	Human monoclonal antibody	Human monoclonal antibody	PEGylated Fab' fragment of humanized antibody
Mode of action	TNF inhibition	TNF inhibition	TNF inhibition	TNF inhibition	TNF inhibition
Approved dosage	3mg/kg every 8 week	50mg once a week	40mg every 2 weeks	50mg once a month	200mg every 2 weeks
Administration	i.v.	s.c.	s.c.	s.c.	s.c.

Figure 2 - TNFalpha inhibitors approved for the treatment of RA. (15)

The main deterrent for the widespread use of TNFalpha inhibitors is their price and consequently their cost-effectiveness. In the United States, the average daily cost of a biologic is $45 compared with only $2 of csDMARDs (38). In 2015, Remicade® the reference infliximab product had a list price in The Netherlands of €602.43 per vial of 100mg(39).

The debate about the cost-effectiveness of TNFalpha inhibitors is a recurrent theme, mainly because most economic evaluation only show cost-effectiveness when the willingness to pay (WTP) is of 50,000–100,000 €/Quality-adjusted life years (QALYS) among patients with insufficient treatment response to cDMARD but not in cDMARD naïve patients. Among patients with an inadequate response to cDMARDs, biologics were associated with an incremental cost-effectiveness ratio (ICERs) ranging from 12,000 to 708,000 €/QALY, with no clear difference in cost-effectiveness between biologic used(40).

1.2.3. Biosimilar DMARDs

A biosimilar medicine is a biological medicine that is developed to be “similar” to an existing biological medicine, they are not generic drugs, which have simpler chemical structures and are identical to their reference medicines. The active substance of a biosimilar and its reference medicine are essentially the same biological substance, but with some minor structural differences, that result from their complex nature and production methods. These biosimilar drugs must be approved by the European Medicines Agency (EMA) and will follow the same rigorous regulatory assessments as all other biopharmaceuticals. If the reference drug has been authorised in the EU for several years, and its clinical benefit is well established, some studies carried out with the reference medicine may not need to be reproduced for the biosimilar(41). Once, and if, a market authorization is granted through this centralised procedure the biosimilar drug will be valid in all EU member states(42).

Until 2016, four bsDMARDs have been approved for the treatment of RA, as displayed in Table 2.

Medicine Name	Active Substance	Authorization Date
Benepali®	Etanercept	14/01/2016
Flixabi®	Infliximab	26/05/2016
Inflectra®	Infliximab	10/09/2013
Remsima®	Infliximab	10/09/2013

Table 2 - BsDMARDs approved for the treatment of RA.

Source: EMA

Since the quality, safety and effectiveness of this drugs are “similar” to the reference drug the question about switching, interchangeability and substitution arises and is subject to debate across Western European countries.

In the case of infliximab biosimilar, there is a clear divide in standing, with some countries with a more “pro-switching” approach like Norway, Denmark, Netherlands and Germany, and the more “resistant” markets such as France, Italy, and Portugal, as noted in figure 3. The main reason for this disparity is not necessarily the “discount rate”, which is the percentage of the biosimilar price reduction when compared to the initial originator price, since although some countries present approximately the same “discount rate” there are still significant differences in the level of biosimilar uptake (e.g. Spain and The Netherlands)(43). The main reason appears to be the lack of data and experience with biosimilar infliximab and the ethical questions raised by switching a stable patient to a biosimilar purely for economic reasons(43).

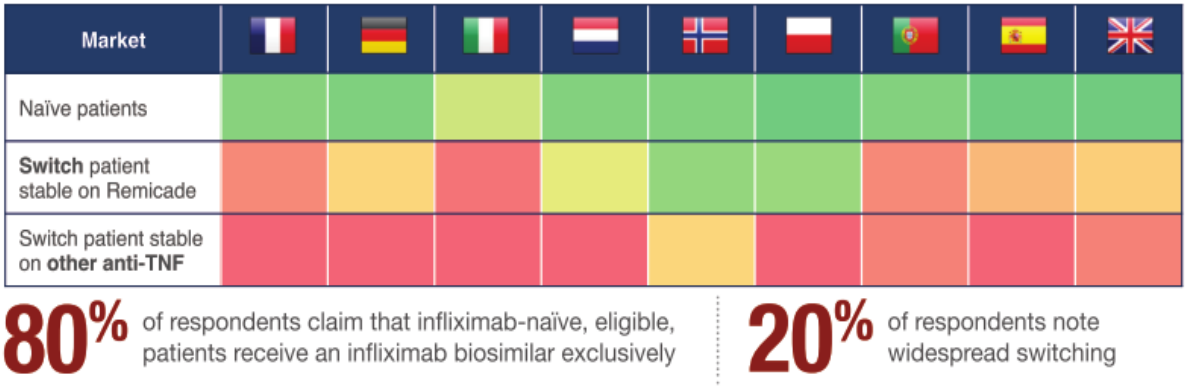

Figure 3- Likelihood of Infliximab Biosimilar prescribing, answers presented on 1-5 rating (Green-5/Red- 1). (43)

There is no uniform “discount rate” for biosimilars in European countries since it varies greatly according to each country’s biosimilar policy that defines the maximum price for the first generic drug that will enter the market, as we as we can observe in annex 3. Portugal defines drug pricing according to rules and criteria set for non-generics (international reference pricing), based on the average ex-factory price observed in the 3 reference countries and sets as a maximum value 80% of the ex-factory price set for the biological medicine of reference(44). The Netherlands reference price for a biosimilar is set in the same way as for all other medicines, using external price referencing of four reference countries(45). Discounts rates for biosimilars are on average 25%, but it can reach up to 70%(43,46).

Another important factor that must be taken into consideration is the delay that exists between the patent expiration date and the first sale of the biosimilar drug. It is always advisable to have the biosimilar enter the market as soon as possible since it allows health professionals time to adapt to the new product and to change clinical guidelines.

Portugal was quick to implement biosimilars of infliximab as a therapeutical option for rheumatic patients, with their first recorded sale in 2013, while the Netherlands first sale was only in 2015(47). It is very difficult to determine exactly how much money biosimilars save in the treatment of RA patients, but according to a study published by Jha. Et al(39), the estimated drug expenditure savings generated in the first year after the introduction in the Netherlands of the biosimilar Remsima® with a “discount rate” of 30%, an uptake of 25% in patients that perform switching from Remicade® and a 50% utilisation in the naïve patients, would be approximately 0.722 million euros. When taking into account that the “discount rate” for biosimilars of infliximab is currently approximately 37% and 50%(43,46), in Portugal and in the Netherlands, respectively, we start to understand how in the future biosimilars will improve our ability to save resources and increase the number of RA patients under biologic therapies.

1.2.4. Treatment strategies for RA

There is a great variety of data regarding clinical and observational trials on drugs and strategies for RA, but all this information also results in some inconsistencies that confuse patients and rheumatologists, resulting in poor decision making when selecting therapeutic strategies for this disease. This has led the EULAR to develop management guidelines for RA, the first in 2010 and later on its update in 2013 (32,36). The Netherlands and Portugal have their own guidelines for the treatment of RA, dating back to 2009 and 2011, respectively, and both derive in from the EULAR guidelines previously mentioned (48,49).

1.2.5. EULAR guidelines for the therapeutical management of RA

The 2013 recommendations reflect the balance of efficacy and safety of DMARDs, with little emphasis on the toxicity of these drugs, as it can be seen in annex 4. As included in the previous guideline of 2010, treatment should start with DMARDs, MTX if possible, as soon as the diagnosis of RA is confirmed and in patients with insufficient response to MTX and/or other sDMARDs with or without GCs, bDMARDs, particularly TNFalpha inhibitor, should be added(33,37). Several studies have demonstrated the efficacy and safety of biologic drugs in RA patients particularly in combination with MTX, although it should be noted that monotherapy is not advisable as a first treatment option(36).

The 2013 guideline also includes the possibility of biosimilar use, although it doesn't explicitly instruct readers on which option, reference product vs biosimilar, to use. The definition of remission has also been altered and is now by the ACR/EULAR published criteria(50), instead of the Disease Activity Score based on 28 joint counts (DAS28), used in previous guidelines.

1.2.6. Portuguese guidelines for the use of biological agents for RA

The Portuguese Society of Rheumatology (SPR) presented a guideline with the purpose of establishing criteria for the introduction and maintenance of biological agents, as well as the contraindications and procedures in the case of non-responders. Some of the criteria used have close similarities to the EULAR 2010 guidelines as it was published one year after said document. The criteria proposed were(49):

1) "Patients who fail or have an inadequate response to cDMARDs are eligible for treatment with biological therapies. To determine the response as inadequate, a patient must present one of the following situations:
    a) DAS ≥ 3.2 or
    b) 2.6 ≤ DAS < 3.2 and worsening of health assessment questionnaire (HAQ)≥0.22 (6/6M) or worsening x-ray scores: Larsen ≥6/SvdH ≥5 (12/12M)

2) Patients with an inadequate response to MTX used in a stable dose of at least 20 mg/week, orally or parenterally, for at least 3 months, may proceed with biological therapy, particularly in patients with severe prognostic markers, or may consider further treatment with another cDMARD or association of cDMARDs during at least 3 months before starting a biological agent, preferably in patients without a severe prognosis.
3) In the case of intolerance, toxicity or refusal to take MTX, the patient may be considered eligible for treatment with a biological agent if there is an inadequate response after a period of at least 3 months of treatment with another cDMARD or an association of cDMARDs".

1.2.7. Netherlands guidelines for the use of biological agents for RA

The treatment of RA in the Netherlands is described in the Kwaliteitsinstituut voor de Gezondheidszorg CBO (CBO)/Nederlandse Vereniging voor Reumatologie (NVR) guideline published in 2009, the international EULAR guideline of 2013(37) and the 2014 directive of the Dutch Society for Rheumatology. And thus, it retains the basic principles of initial therapy of RA with csDMARDs and glucocorticoids. If this therapeutical approach doesn't reach intended therapeutically target, DAS28> 3.2, in patients treated for a sufficient time period bDMARDs may be considered(48).

1.3. Dutch healthcare system:

The healthcare system in The Netherlands is operated by private health insurances companies that comply with certain public social conditions expensed under the "Health Insurance Act" of 2006. It is mandatory for all residents to enrol on a basic health insurance which consists of a standard package of insured services. Insured patients have the right to reimbursement for medicinal products included in the positive list of the Drugs Remuneration System (DRS). The "preference policy" states that health insurers are obliged to appoint at least one medicinal product of all the medicinal products with the same active substance available within the positive list DRS. In the inpatient setting, where biologic drugs such as TNFalpha inhibitors are dispensed since 2012, the availability of medicinal products used in a given hospital is decided by each hospital's administration board and has their expenses covered by the health insurances according to each diagnosis treatment combination (DTCs)(51).

The Dutch healthcare system has been under a hot debate during the last decades, mainly due to the high public expenditure required to keep the system running. Despite this, there seems to be a consensus regarding the high quality of service and good health outcomes that patients can expect. A poll conducted in 2013, showed that 91% of the population evaluate the quality of the healthcare system in the Netherlands as good, with 43% still saying that there was still a need to implement further reforms(52).

1.3.1. Pharmaceutical Expenditure

Expensive innovative drugs, such as TNFalpha inhibitors, and an ageing population, who commonly suffer from one or more comorbidities, are serious challenges that may affect the sustainability of the Dutch healthcare system. To solve this problem a reform was implemented in 2012, aimed at the prospect of transferring many expensive drugs from retail to the hospital sector, increasing the bargaining power of hospitals and consequently leading to the purchase of pharmaceuticals at inferior prices. TNFalpha inhibitors were the first to be transferred in 2012, followed by expensive cancer medicines and growth hormones in 2013, fertility hormones in 2014 and the remaining cancer medicines in 2015(53). Hospitals were compensated for the costs of these transferred medicines and had to agree with a fixed annual growth rate of expenditure of 1.5% in 2014, followed by 1% fixed annual growth until 2017. But expensive medicines have an expenditure growth rate far greater than the agreed growth rate, for example, the prices of new cancer medicines increased by 80% between 2011 and 2014, putting into question the feasibility of the agreed growth in hospital expenditure. Indeed, in 2015, several hospitals complained to the Dutch Broadcast Foundation that they were no longer able to finance expensive medicines, even warning that their financial situation could jeopardise public access to these medicines. There were even reports of several clinicians confessing that their hospitals had rationed the use of expensive medicines(53).

1.4. Portuguese healthcare system

The Portuguese healthcare system is characterised by three coexisting, overlapping systems: The National Health Service (NHS), special public and private insurance schemes for certain professions (health subsystems), and private voluntary health insurance(VHI)(54). All residents in Portugal have access to healthcare provided by the NHS, financed mainly thru taxation. The existence of three different systems allows patients to benefit from triple coverage, that is, from the NHS, a health subsystem from their job and VHI. Pharmaceutical co-payment of retail dispensed prescribed drugs, under the NHS, is divided into four categories, category A has a reimbursement rate of 90% of the costs; category B, 69%; category C, 37%; and category D, 15%(54). TNFalpha inhibitors and many other drugs are excluded from this regiment and when prescribed for certain diseases, such as RA, the drug is 100% insured(54). These drugs, when prescribed by a rheumatologist in a specialised consultation, must be dispensed by the hospital pharmacy of the NHS with the costs being supported by the hospital or by their respective regional health administration (RHA)(55).

1.4.1. Pharmaceutical Expenditure

Portugal's Health expenditure has steadily reduced since the financial assistance of 2011 by "Troika", which encompasses the European Commission (EC), the International Monetary Fund (IMF) and the European Central Bank (ECB). This reduction was conducted due to an excessive health expenditure as a percentage of GDP when compared to the EU's average of 9.5% in 2011(56). This reduction was particularly hard to accomplish because of two main reasons, first, treatment options tend to be more complex and costly to a population, that due to ageing, requires more medical treatments. Secondly, due to the financial crises, Portugal's GDP decreased by around 5% between 2008 and 2013, making it necessary to compensate said decrease with an even bigger budget cut for health. Nevertheless, a great reduction in total health expenditure as a percentage of GDP was accomplished, and in 2013 it reached 9,6%, almost identical to the EU average of 9,5%. But some signs of fragility on an already stressed system are starting to appear. The hospital sector which is taking the full brunt of the increasingly priced medication, such as immunomodulators and cancer drugs, is a clear example of this(57). Hospital debt rose by 27 million euros per month in 2016, and although this debt is not all pharmaceutical-related, it is estimated that the sum of all hospital debt to the pharmaceutical industry in 2016 is around 1.100 million euros(58,59).

1.4.2. Regional differences in health providers

Portugal is a country with big regional differences in educational, income, healthcare, and many others. These factors tend to privilege citizens that live near the coastal area, particularly in the central and northern regions. This inequality also has a big impact in patients with RA, since this disease is more prevalent in older individuals that tend to live in areas with fewer care providers. Figure 4 shows a clear geographical asymmetry on the estimated prevalence of undiagnosed patients, with some interior regions of Portugal being highlighted as having up to 70% of the total number of rheumatic patients, undiagnosed.

In 2006 the European proportion of registered rheumatologists per inhabitant was around 1:60.000, with Portugal and The Netherlands on the lower end of the spectrum with 1:100.000 and 1:80.000, respectively, and France and Estonia on the upper end with 1:25.000 and 1:35.000, respectively(60). In Portugal, the total number of rheumatologists has been increasing, with the intent of reaching the mark of 1:50.000(61). From 2008 to 2013 the proportion varied from approximately 1:95.000 to 1:72.000, respectively. However, it still looks that some regions, mainly Trás-os-Montes, Beira Interior or Algarve, are lagging behind the rest of the country due to an inferior amount of healthcare centres and an average of only 1 to 3 rheumatologists per centre(61).

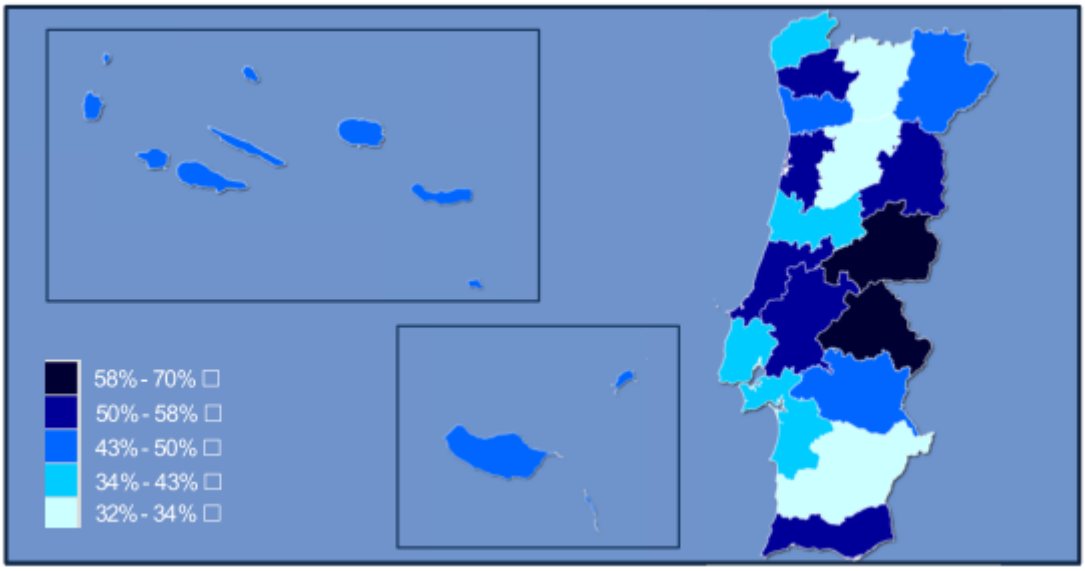

Figure 4 - Estimative of the percentage of undiagnosed patients with rheumatic diseases. (61)

2. Objectives

2.1. General Objective

Determine the variation in TNFalpha inhibitors utilization by RA patients in Portugal and in The Netherlands between 2008 and 2013.

2.2. Specific Objectives

1. Describe the main differences between treatment guidelines of RA in both countries;
2. Assess the evolution of TNFalpha inhibitors utilization and patient's access to biologic drugs between 2008 and 2013;
3. Identify the possible reasons for usage and access variation of TNFalpha inhibitors in Portugal and in the Netherlands.

3. Methodology

This is a descriptive, retrospective and observational study that compares biological drug usage between Portugal and the Netherlands, within the class of TNFalpha inhibitors drugs. Countries were selected due to their similarity in population size and characteristics (e.g. age pyramid) and due to their differences regarding geographical location, GDP per capita, health expenditures and biologic distribution channel (% of hospital sales or retail).

3.1. Country and patient characteristics, biologic drug access determinants and treatment guidelines

Population characteristics such as population size, demographics and RA prevalence, economic and expenditure factors such as GDP per capita, total health expenditure and medical goods expenditure and treatment guidelines were retrieved from a variety of sources (6,48,49,62–66). Rheumatologists per 100.000 inhabitants were determined according to the information provided by the NVR and by the Portuguese Order of Doctors(67).

Characteristics of patients under therapy with biologic therapy in 2016 were determined according to the "Registo Nacional de Doentes Reumáticos" (Reuma.pt) 2016 report and University Medical Center Utrecht, for Portugal and the Netherlands, respectively. Reuma.pt is the Portuguese national registry for rheumatologic patients, with 16378 patients registered in 2016, of which 40.73% (6630 patients) were diagnosed with RA (68). The University Medical Center Utrecht is the main hospital of the city of Utrecht, located in the Province of Utrecht in the Netherlands, that at the time of this analysis had 1274 patients undergoing biologic therapy with the following TNFalpha inhibitors: L04AB01 - etanercept, L04AB02 - infliximab, L04AB04 - adalimumab, L04AB05 – certolizumab pegol, L04AB06 - golimumab.

To guaranty maximum comparability of RA prevalence in both countries, Kobelt et al(19) report was utilised.

3.2. Utilisation data

Table 3 provides an overview of the data sources for the utilisation data of TNFalpha inhibitors utilisation data in Portugal and the Netherlands.

Usage data for Portugal represent the total consumption in all public hospitals in the country and it was presented according to the "Código Hospital Nacional do Medicamento" (CHNM), which identifies all medication with a specific and unique code, that doesn't differentiate between the original drug and its generic/biosimilar counterpart.

For the Netherlands, two sources of utilisation data were used, namely, the GIPdatabank, which contains information about outpatient care provided and paid in accordance with the Health Insurance Act(69) and the report "Evaluatie overheveling geneesmiddelen" by Erf et al.(70) which contains information on the national utilisation of these biologics shared by the Zorginstituut Nederland (ZIN).

No accurate data on L04AB02 – infliximab utilisation was present in either Dutch databases and thus it was excluded from the analysis. Drug utilisation was measured using Anatomical Therapeutic Chemical Code (ATC)/DDD methodology since it functions as a common unit of consumption independent of drug price and dosage form(71,72). For the selected drugs, the

DDDs are as following: infliximab – 3.75mg; etanercept – 7mg; adalimumab – 2.9mg and golimumab – 1.66mg. DDDs were calculated according to the usual dose indicated for RA on each products' Summary of Product Characteristics (SPC)(73–76). Utilisation is presented in DDDs/1000 inhabitants/day and it was calculated according to the number of inhabitants of each country on the 1st of January of each year.

	Portugal	Netherlands
Data Source	INFARMED – Autoridade Nacional do Medicamento e Produtos de Saude, I.P.	GIPdatabank (70) Erf. et al(69)
Period of drug utilisation data	2008 to 2013	2008 and 2009 - Gipdatabank 2010 to 2013 – Erf et al(69)
Drugs under analysis ATC	2008-2011	2008-2009
	Etanercept (L04AB01) Adalimumab (L04AB04)	Etanercept (L04AB01) Adalimumab (L04AB04)
	2011-2013	2010-2013
	Etanercept (L04AB01) Adalimumab (L04AB04) Golimumab (L04AB06)	Etanercept (L04AB01) Adalimumab (L04AB04) Golimumab (L04AB06) Anakinra (L04AC03) Ustekinumab (L04AC05)
Drug utilization ATC/DDD	Etanercept – 7mg Adalimumab – 2.9mg Golimumab – 1.66mg	

Table 3- Overview of the utilisation data of TNFalpha inhibitors in Portugal and the Netherlands.

3.3. Patient access to biologics

Patient access to biologics (PAB) is a variable calculated according to the following ratio(4):

$$P_{AB} = \frac{Rheumatic\ patients\ treated\ with\ biologics}{Total\ prevalence\ of\ RA} \quad (1)$$

PAB is a measure that allows to quantify and compare biologic drug consumption while accounting for the total prevalence of a given disease in a given country.

The number of patients treated was obtained via INFARMED – Autoridade Nacional do Medicamento e Produtos de Saude, I.P and GIPdatabank, for Portugal and the Netherlands, respectively. To account for the different possible therapeutically indications of biologic drugs, the following shares were estimated for etanercept, adalimumab and infliximab, 75%, 53% and 39%, respectively, as done in previous works(4). All other drugs were accounted as having only RA as a therapeutic indication.

4. Results

4.1. Countries characteristics

Table 4 shows a summary of four main group of factors under analysis between 2008 and 2013. Both countries possess a considerable percentage of citizens aged 65 or more, with Portugal leading with 19.6% in 2013, above the EU average of 18.3%. GDP per capita has decreased in both countries since 2008, but there remains a big gap in GDP per capita between both countries, with the Netherlands GDP reaching 51.425$, more than double Portugal's 21.619$, in 2013.

Health expenditure as a percentage of GDP in both countries was above the EU average of 9.0% and 9.5%, for 2008 and 2013, respectively. In fact, the Netherlands, total health expenditure increased from 9.6% to 11.0%, during this period, while Portugal's percentage decreased from 9.9% in 2008 to 9.6% in 2013. Since GDP varied greatly during this period figure 5 was developed to illustrate the variation in health expenditure in millions of dollars during the analysed period, in it is possible to observe that the health expenditure in Portugal remained relatively stable, while the Netherlands health expenditure increased slightly until 2011, with a more significant increase in the two following years.

Medical goods expenditure as a percentage of total health expenditure decreased in both countries, with a 5% decrease in Portugal during the research period and culminating in a percentage of 19.7% in 2013, compared to the Netherlands 12.2%. Retail and Hospital distribution of TNFalpha inhibitors was conducted in the Netherlands until 2012, being followed by the transition to a hospital distribution channel only. Portugal, on the other hand, maintained a hospital distribution channel through the research period.

No significant differences were observed in the treatment guidelines of both countries, but it should be noted that only on the Dutch guidelines appear to be some flexibility regarding the initiation of bDMARDs therapy with a DAS28 score inferior to 3.2.

A greater prevalence of specialized health professionals was observed in the Netherlands, that in 2013 presented a ratio of 1.71 rheumatologists per 100.000 inhabitants, compared to Portugal's ratio of 1.37.

	Netherlands 2008 - 2013	Portugal 2008-2013	European Union 2008-2013
Population characteristics			
Population (millions)(64)	16.4 – 16.8	10.6 – 10.5	496.0 – 500.9
Population aged 65 years and over (% of total population)(63)	14.9 - 17.1	17.9 – 19.6	17.2 – 18.3
Prevalence RA (%)	0.46	0.47	-
Economy and expenditure			
GDP per capita in US$(63)	56.929 – 51.425	24.816 - 21.619	37.844 - 35.240
Total health expenditure (% of GDP)(63)	9.6 – 11.0	9.9 – 9.6	9.0 – 9.5
Total health expenditure (million $)(63)	60.680 – 71.132	16.729 – 15.476	-
Medical goods expenditure (% of total health expenditure)(62)	15.1 – 12.2	25.0 – 19.7	-
Pharmaceutical expenditure, (PPP$ per capita)(63)	4427 - 5170	2584 - 2634	3033 - 3419
Biologic drug access determinants			
Rheumatologist per 100.000 habitants	1.61 – 1.71	1.05 - 1.37	-
Distribution channel	Hospital and retail (2008-2011) Hospital (2012-present)	Hospital	-
Treatment Guidelines(48,49)			
Treatment initiation	One csDMARD	One csDMARD	One csDMARD
Criteria required to initiate TNFalpha inhibitors	"DAS ≥ 3.2 or 2.6 ≤ DAS < 3.2 and worsening of HAQ≥0.22 (6/6M)9 or worsening x-ray scores: Larsen≥6/ /SvdH ≥5 (12/12M)10"	"DAS ≥ 3.2 or 2.6 ≤ DAS < 3.2 and worsening of HAQ≥0.22 (6/6M)9 or worsening x-ray scores: Larsen≥6/ /SvdH ≥5 (12/12M)"	-

Table 4 - Countries characteristics, biologic drug access determinants and treatment guidelines between 2008 and 2013.

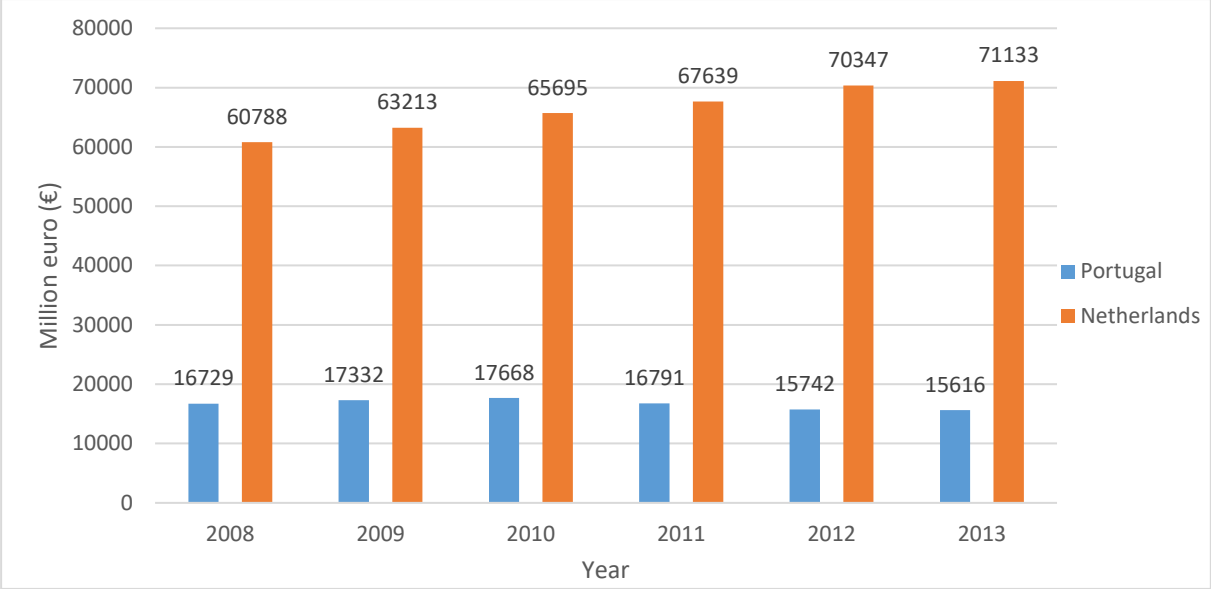

Figure 5- Total health expenditure in millions of dollars, in Portugal and the Netherlands, during the period between 2008 and 2013. **(64)**.

Figure 5 represents with more detail the evolution of total health expenditure in both countries. Portugal's expenditure stabilized until 2011, followed by a significant decrease in 2012 and 2013. Netherlands, on the other hand, displayed a continues growth in expenditure, having increased around 15% of its total value in just five years.

Table 5 presents an analysis of the gender and age of patients enrolled in biologic therapy in the Netherlands and in Portugal. Dutch patients under biologic therapy appear to be, on average, younger than Portuguese patients, particularly when undergoing therapy with the two main subcutaneous TNFalpha inhibitors, etanercept and adalimumab. A higher percentage of female patients compared to male patients was detected in both countries, with Portugal presenting the biggest gender disparity of around 2:1.

	Netherlands	Portugal
Gender		
Female / Male (%)	57.5 / 42.5 (N= 1274)	66.06 / 33.94 (N = 4284)
Age		
Mean age of patients under biologic treatment	43.92 ± 20.56 (N = 1274)	51.18 ± 16.82 (N = 4284)
Mean age of patients under Infliximab treatment	-	52.51 ± 15.61 (N = 415)
Mean age of patients under Etanercept treatment	42.65 ± 22.93 (N = 313)	50.3 ± 17.27 (N = 1457)
Mean age of patients under Adalimumab treatment	43.68 ± 20.11 (N = 862)	48.13 ± 16.62 (N = 915)
Mean age of patients under Certolizumab Pegol treatment	54.53 ± 12.51 (N = 17)	48.76 ± 14.04 (N = 40)
Mean age of patients under Golimumab treatment	49.92 ± 20.56 (N = 82)	50.45 ± 13.24 (N = 452)

Table 5 - Rheumatic patients' characteristics of Portugal and The Netherlands in 2016

4.2. Utilisation Data

An increase in TNFalpha inhibitors has been noted in both countries, as noted in Figure 6. In Portugal, drug utilization increased from 0.18 DDDs/1000 inhabitants/day, in 2008, to 0.46 DDDs/1000 inhabitants/day, in 2013. The Netherlands also displayed an increase from 0.98 DDDs/1000 inhabitants/day, in 2008, to 1.64 DDDs/1000 inhabitants/day, in 2013. This latter increase resulted in a widening gap in drug utilisation between both countries, with the Netherlands having a surplus of around 0.80 DDDs/1000 inhabitants/day, in 2008 and of 1.19 DDDs/1000 inhabitants/day, in 2013, when compared to Portugal's utilisation during this period.

PAB, as observed in figure 7, also increased in both countries, with a more notable increase in the Netherlands, which improved its PAB by approximately 20% between 2008 and 2013. While in Portugal, during the same time period, it increased around 4%. By the end of 2013, only approximately 7% of all Portuguese citizens afflicted with RA had access to TNFalpha inhibitors.

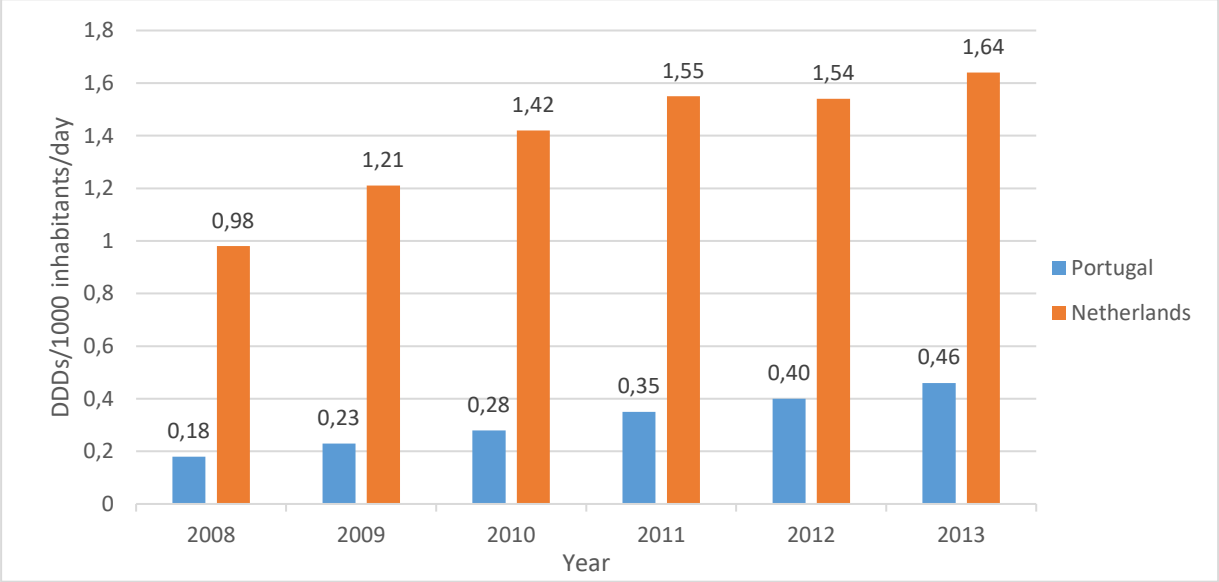

Figure 6- Utilisation of TNFalpha inhibitors in DDDs/1000 inhabitants/day, between 2008 and 2013 in Portugal and the Netherlands.

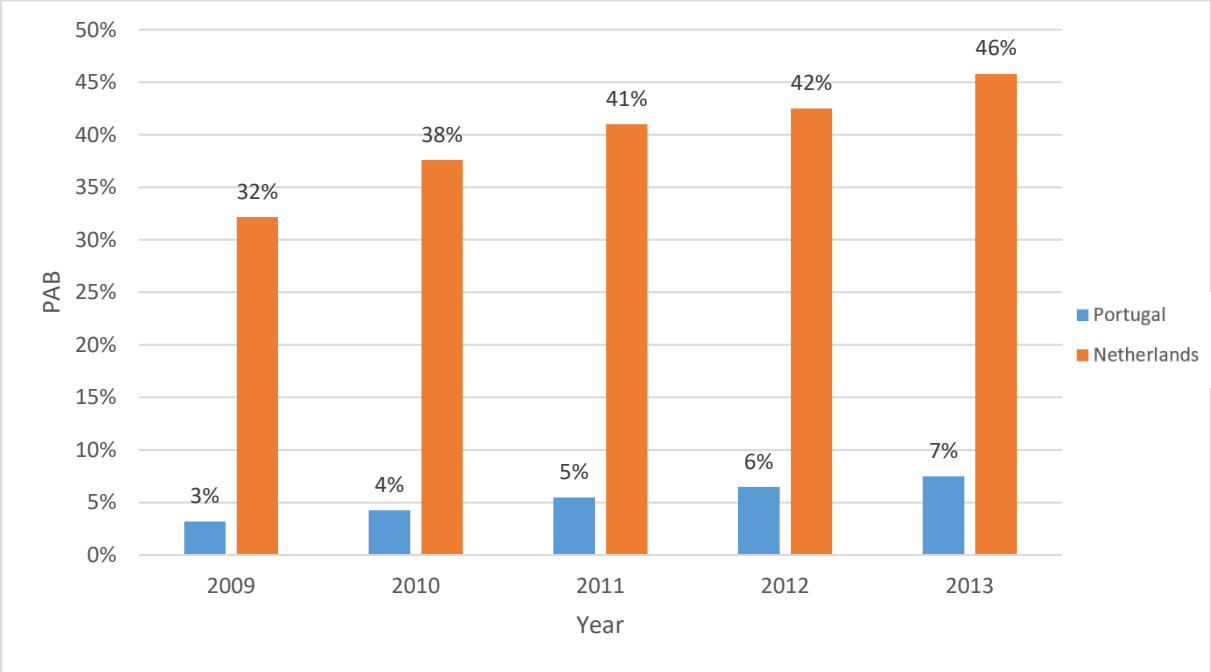

Figure 7- Patient access to biologics, between 2008 and 2013 in Portugal and in the Netherlands.

5. Discussion

This analysis indicates that there is a significant difference of TNFalpha inhibitors utilisation between the selected countries. As demonstrated in previous works(5), this difference in utilization appears to be increasing at a steady rate, even when the difference between the main factors correlated with an increased drug usage, in both countries, remained relatively constant. Health expenditure and GDP per capita, still seem to be two major factors that contribute to the expansion of biologic therapy use, but as seen during the analysed period, the influence of such factors on drug utilisation must be reevaluated. In both countries, GDP per capita and medical goods expenditure decrease significantly, and, in Portugal, this decrease was also accompanied by a decrease in health expenditure as a percentage of GDP, but still, an expansion of TNFalpha utilisation and PAB did occur.

Health expenditure in millions of dollars remained relatively constant in Portugal between 2008 and 2013, despite the increasing utilisation of TNFalpha inhibitors during this period. In the Netherlands health expenditure in millions of dollars increased slightly until 2011, the period in which utilisation increased more drastically, and then after 2011, a bigger increase in health expenditure was accompanied by a stabilization in drug utilisation as illustrated in figure 6. In fact, these results suggest that an increase in clinical efficiency and drug pricing renegotiation might have been conducted in Portugal, otherwise, it would have been very difficult to maintain such access to biologics while still maintaining such a reducing in expenditure with medical goods. In the Netherlands, this might have been also the case, due to the reduction in medical goods expenditure, but possibly to a lesser extent.

Distribution channel, another factor argued to influence the utilisation of biologic drugs(4), also displayed a limited impact in TNFalpha utilisation, as noted in the Netherlands during the period of 2012 to 2013, where utilisation kept rising even after the transfer of biologics to a hospital only distribution channel in 2012. Granted that in 2012 a slight decrease in biologic utilisation occurred, but it was mainly due to a decrease in patients' dosages, from an average of 301 DDD per user, in 2012, to an average of 287 DDD per user, in 2013(70). While this alteration in dosages seems to have caused no significant impacted on patient health outcomes(70), it appears to have temporarily slowed down the increased in TNFalpha inhibitors utilisation.

Treatment guidelines in both countries present limited differences, particularly when regarding the criteria required to initiate bDMARDs. However, there is a possible variation regarding the

adherence of clinicians to these guidelines, as noted in previous works, where Portuguese clinicians seem to have a somewhat limited adherence to clinical guidelines(5).

As noted in previous works, there are multiple determinants of bDMARDs utilisation in Western European countries, such as GDP per capita, distribution channel, prevalence and total health expenditure(4,5). The fact that most of these determinants had their value decrease or stabilise during the entire analysed period, while TNFalpha inhibitors consumption kept on rising, is somewhat contradictory to what has been previously established in previous works(4,5). Some other factors were surely involved, other than biosimilar drugs since these were only introduced in 2013 and had no time to cause a significant impact on drug utilisation.

Another important factor may also be used to explain this phenomenon of TNFalpha inhibitors utilisation and access in both countries, the number of rheumatologists per 100,000 inhabitants, which increased in both countries during the research period. The Netherlands displayed a greater ratio of rheumatologists per 100,000 inhabitants than Portugal, both in 2008 and in 2013, and as now surpassed the 1.67 ratio preconized as the required for European countries(77). Portugal, despite the considerable distance from the standard of 1.66, has also shown some progress and is now closer to meet this international standard. An increase in the number of rheumatologists may have led to a growth in RA detection and treatment, indirectly contributing to the observed upsurge of TNFalpha utilisation. Unfortunately for Portugal, the ratio of rheumatologists per 100,000 inhabitants is not enough to measure the real difficulty that patients face when trying to contact with specialists. Due to its severe desertification of the interior regions, it is estimated that some regions have 58% to 70% of all rheumatic patients(61). Further increases in the number of a rheumatologist in Portugal may serve to attenuate this problem, but such measures will continue to have limited success on the overall drug utilisation of the country unless the problem of desertification is properly tackled.

Mean age of patients under biologics in both countries also shows some noteworthy differences, Portuguese patients under bDMARDs therapy are, on average, older than their Dutch counterparts. This is likely due to a later diagnosis of RA paitiens in portuguese, as a consequence of the elevated number of undiagnosed patients in certain regions of the contry and of a lesser willingness to transition from csDMARDs to bDMRDS. Either scenario results in poor patient prognosis and in higher patient morbidity, as stated by EULAR(31). There should be noted that contrary to all other users of biologic drugs, Dutch patients under certolizumab pegol treatment appear to be older than their Portuguese counterparts, but this might be due to the smaller sample size of 17 and 40 patients for the Netherlands and Portugal, respectively.

It’s reasonable to assume that TNFalpha inhibitors utilisation will continue to increase, perhaps at a faster rate than that observed between 2008 and 2013, without causing a major impact on health expenditure. The impact of biosimilar drugs will be crucial to accomplish this result and all evidence indicates that it will be the case, especially when taking into account the prediction that drug expenditure with RA in the Netherlands could be reduced by 0.722 million euros in the first year after the introduction of one of its biosimilar drugs, Remsima®(39).

Some limitations of this study should be noted. Dutch patient characteristics as presented in this work may lack nationwide representability since they were inferred from the analysis of a sample composed of a single hospital. The patients included where not differentiated according to diagnosis and thus there is the possibility that other non-rheumatic diseases might have affected the mean age of patients obtain. Prevalence data dates from Kobelt et al.(19) may be somewhat underestimated when considering the demographic shift present in Western European during the current decade, there is also the question regarding the now outdated diagnostic tools utilised by Kobelt et al.(19) that predate the new ACR/EULAR classification criteria. The DDD methodology does not necessarily replicate the clinical dosages of each pharmaceutical formulation, but it is also important to note that the difference does not account for a big variation in results. The fact that utilisation data of the Netherlands was only available on a aggregated form, lead. There is also an overrepresentation of TNFalpha inhibitors utilisation and PAB for RA since it was assumed to be the sole therapeutically indication of these drugs, which is not the case. But, as stated in previous works, RA is the main indication of TNFalpha inhibitors(5). Utilisation data of TNFalpha inhibitors in the Netherlands is lacking and in many cases incomplete, particularly after the transition of all TNFalpha inhibitors to the Hospital sector. This transfer resulted in some difficulties when trying to assert the full extent of drug utilisation, particularly for infliximab, which lead to the exclusion of this drug from this analysis. This has resulted in an underestimation of the entire utilisation of TNFalpha inhibitors in the Netherlands and Portugal since infliximab is one of the three most utilized TNFalpha inhibitors, of which around 30% of the total usage is estimated to be in the treatment of RA(4). Despite this limitation, it is still possible to draw some important conclusions about the way TNFalpha inhibitors utilisation varied in the Netherlands during the period 2008 and 2013.

6. Conclusion

In conclusion, this study displays the remarkable improvement in TNFalpha inhibitors utilisation, measured in DDD's utilised, in Portugal and in the Netherlands, despite the difficult conditions imposed by the recent economic recession. However, the increasing gap in biologic utilisation in between both countries is a real reason for concern. This gap is accentuated when we the mean age of patients under biologic therapy is considered

It is time to reshape national priorities and policies to revert this increasing gap in bDMARD utilisation, or else Europeans will start to face growing discrepancies in health access that soon may not be tolerated. Treatment guidelines present small differences in the criteria to initiate biologic treatment, but divergence by practitioners is still questionable, particularly in Portugal.

This variation in utilisation displayed by both countries, between 2008 and 2013, is multifactorial and it should be addressed as such. GDP per capita, health expenditure, distribution channel and treatment guidelines, by themselves, are not enough to explain the dynamic evolution of bDMARDs utilisation, particularly in times of economic recession and austerity measures. Other factors such as the increase in the ratio of rheumatologists per 100,000 inhabitants, amplified clinical efficiency, a reduction of user dosages and a reduction of drug prices are likely to have played a significant role during this period and may serve as an explanation for the increasing utilisation of TNFalpha inhibitors noted during this period.

It must never come a time of one's prospect of having the best available treatment for their condition derives primarily from their nationality and not from their disease status. Biosimilar drugs might help bridge this gap, but it is still unclear if will be sufficient to accomplish such deed.

Netherlands biologic utilisation data quality was subpar when compared to Portugal's data. The lack of reliable publicly accessed information in the former, particularly after 2012, limited this analysis and made it more difficult to fully understand the level of access to biologics in the Netherlands.

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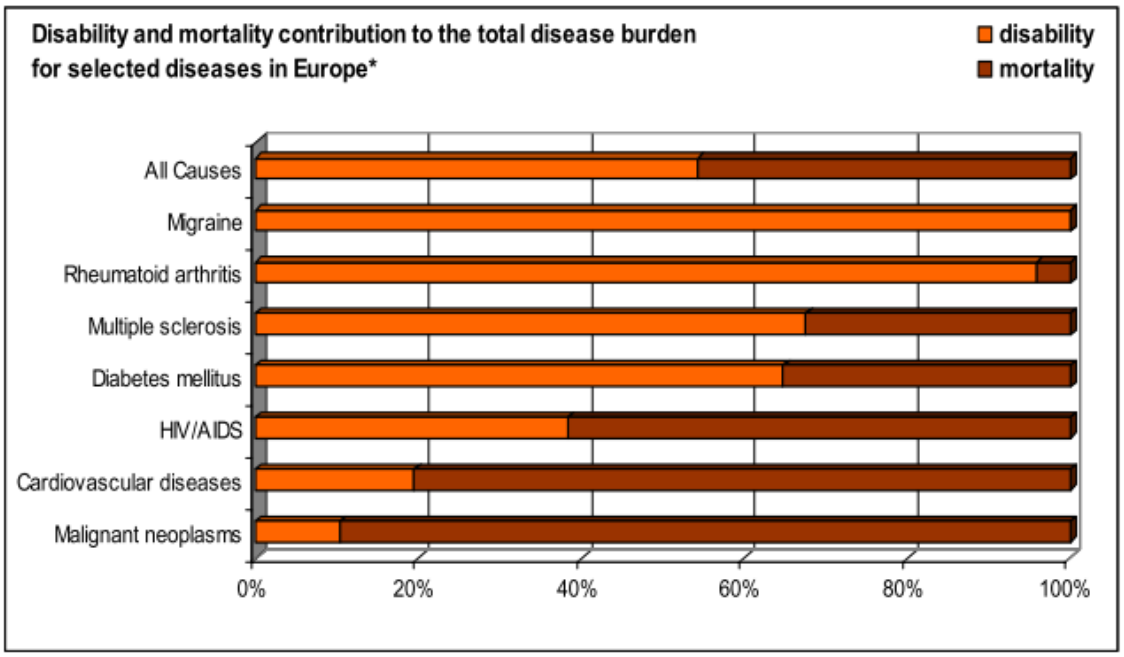
Annexes

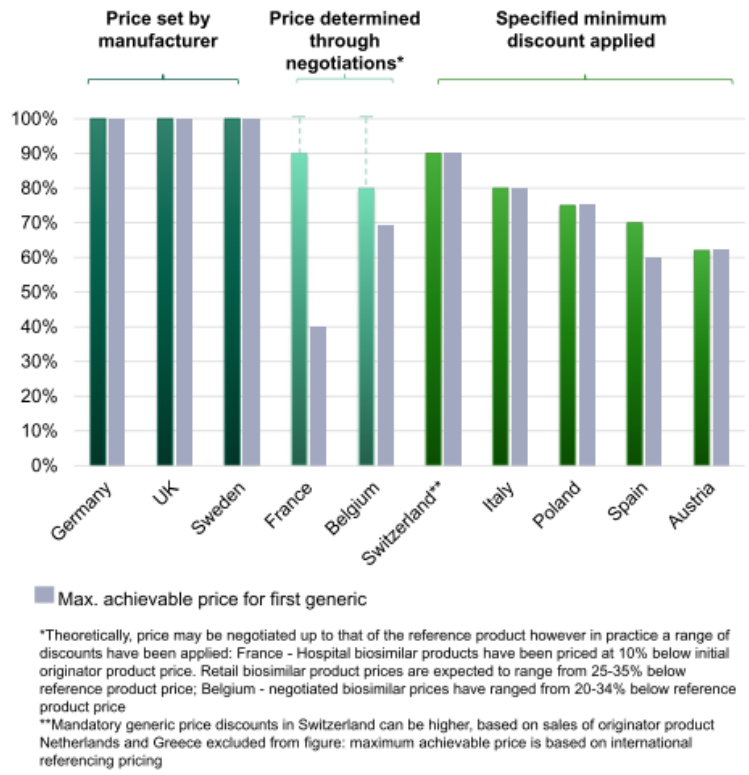
	Women			Men			Total
	20-44	45-64	>64	20-44	45-64	>64	
Total EU 27	157,000	536,000	681,000	64,000	259,000	247,000	1,945,000
W.Europe	125,000	425,000	563,000	51,000	208,000	210,000	1,581,000
E.Europe	32,000	111,000	118,000	13,000	51,000	37,000	362,000
Turkey	25,000	48,000	21,000	11,000	24,000	9,000	138,000

Annex 1: Estimated total number of patients with RA in Europe plus Turkey(19).



**WHO sub-region EUR A (Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Norway, Netherlands, Portugal, San Marino, Slovenia, Spain, Sweden. Switzerland, United Kingdom)*

Annex 2: Share of morbidity and mortality in the disease burden(19).



*Theoretically, price may be negotiated up to that of the reference product however in practice a range of discounts have been applied: France - Hospital biosimilar products have been priced at 10% below initial originator product price. Retail biosimilar product prices are expected to range from 25-35% below reference product price; Belgium - negotiated biosimilar prices have ranged from 20-34% below reference product price
**Mandatory generic price discounts in Switzerland can be higher, based on sales of originator product
Netherlands and Greece excluded from figure: maximum achievable price is based on international referencing pricing

Annex 3: Maximum achievable "discount rate", symbolized by the biosimilar price as a % of initial originator price(78).

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations can be seen in the online supplement or the original publication)

	Overarching principles
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B.	Rheumatologists are the specialists who should primarily care for RA patients
C.	RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2.	Treatment should be aimed at reaching a target of remission or low disease activity in every patient
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4.	MTX should be part of the first treatment strategy in patients with active RA
5.	In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy
6.	In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used
7.	Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
8.	If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered
9.	In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
10.	If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11.	Tofacitinib may be considered after biological treatment has failed
12.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
13.	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14.	When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

*TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA).
†The 'certain circumstances', which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text.
‡Tapering is seen as either dose reduction or prolongation of intervals between applications.
§Most data are available for TNF inhibitors, but it is assumed that dose reduction or interval expansion is also pertinent to biological agents with another mode of action.
DMARD, disease-modifying antirheumatic drug; EMA, European Medical Agency; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Annex 4: 2013 Update of the EULAR recommendations for the treatment of RA(37).