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ΜΑΡΙΑΝΝΑ ΜΗΤΡΑΤΖΑ (MARIANNA MITRATZA)

# "Drug survival and effectiveness in psoriatic patients treated with biological agent for the first time"

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*To my family and friends*

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## Contents

# Chapter 1: Introduction

Psoriasis is a complex, inflammatory, proliferative skin disease with chronic evolution, which is characterized by a systemic response. The socioeconomic impact of this disorder is very high[1]. This “immune-mediated inflammatory disease" has incidence rates that are ranging between 2 and 4% in the general population[2]. In the Greek population the relevant prevalence of psoriasis is estimated at 2.8%[3].

Environmental factors, such as lifestyle, mild trauma and infections, as well as psychological stress can have an impact on the onset or the exacerbation of psoriasis, by activating genetically vulnerable keratinocytes and immune cells through the interplay of several known and unknown pathways[4-6]. Moreover, certain medications such as beta-blockers, lithium salts and non-steroidal anti-inflammatory drugs have been reported for the activation or the progress of the disease[7].

Variants of several genes involved in the axis of the T helper-17-cell/interleukin-23 (Th17/IL-23)[8] and relevant biomarkers on the skin lesions have been identified during the last years of medical research, contributing to the wide development of biologic therapies for the treatment of psoriasis. The NF-kB immune signaling or negative regulators have not been studied in thoroughly as potential therapy pathways[9].

Clinically, typical skin lesions are characterized by erythema, epidermal hyperplasia and scaling, with the histological analyses revealing inflammatory infiltrates and capillary angiogenesis. The lesions are usually located on the extension areas of elbows and knees, and can also include nails (80-90%)[10] and scalp (75-90%)[11], areas that are more difficult to treat. Sometimes they involve the entire body surface area. One large, multinational, population-based survey demonstrated that psoriasis patients perceive their most bothersome signs or symptoms to be itching (43%), scales (23%), and flaking (20%)[12]. Following morphologic criteria, there are plaque (psoriasis vulgaris: chronic plaque psoriasis), guttate, pustular and erythrodermic subtypes of psoriasis[13].

Psoriasis has been associated with various comorbidities, such as metabolic syndrome, obesity, hyperglycemia, major cardiovascular diseases, non-alcoholic fatty liver disease, Chron's disease, lymphoma and depression[8,14-21]. The diagnosis of metabolic syndrome requires central obesity (Body Mass Index: BMI>30 kg/m$^2$) and any two of the following abnormalities: elevated plasma triglycerides, reduced HDL (high-density lipoprotein cholesterol), elevated blood pressure, and raised fasting plasma glucose. The association of psoriasis with metabolic syndrome and its components has been confirmed in large epidemiologic studies[22,23]. Whether these comorbidities occur as a result of common susceptibility genes or as a result of systemic inflammation needs to be further investigated[24,25]. Many inflammation biomarkers are detected in the blood of patients with psoriasis and are associated with disease activity[26]. Moreover, the prevalence rate of undiagnosed psoriatic arthritis among patients with psoriasis is 15.5%[27] and diagnosed manifestations of psoriatic arthritis can reach the level of 48%[28].

Lifestyle conditions, such as alcoholism[29,30] and smoking, have also been associated with psoriasis, although it is not clear whether they derive from the impact of the disease on the quality of the life of patients or is a prognostic factor[31]. Psoriasis-related stress may be involved in the psoriatic exacerbations, and greater stress reactivity has been associated with onset of psoriasis at an earlier age[32].

The huge impact that moderate to severe psoriasis has on the patient's quality of life raised the initial interest for this study. The fact that the treatment framework is changing during the last years from short-term intervention of acute rashes toward long-term management, taking into consideration both the skin symptoms and comorbidities[33] set the basis to investigate the drug survival in psoriatic patients treated with biological agent for the first time. Drug survival is synonymous to the time until the discontinuation of the treatment[34]. This can be caused because of inadequate response (primary or secondary), occurrence of an adverse event or other reason (patient's choice, insurance).

The effectiveness of psoriasis therapies under real-world circumstances also requires further investigation as recent data suggest that psoriasis therapies have limited persistence and lower effectiveness in real-world settings compared with estimates derived from clinical trials[35]. Treatments currently used for psoriasis are first-line topic regimens, second-line therapies such as the

phototherapy either narrowband UVB or bath psoralen ultraviolet A (PUVA) and the systemic drugs methotrexate, retinoids (acitrecin) or cyclosporine. Biologic agents, introduced in 2004, demonstrate immunosuppressant activity and are currently used for patients unable to benefit from first- and second-line modalities, mainly because of their high cost. Antagonists of TNF-a (adalimumab, etanercept, infliximab), and modulators of lymphocyte differentiation mediated by IL-12, IL-23 and IL-17 (e.g. ustekinumab) are the most common, are also approved for psoriatic arthritis and are induced via injection[36]. Biologics are used for long-term treatment, as long as there is no evidence of cumulative toxicity or drug–drug interactions. They have a good safety profile with only a small increase in opportunistic infections[33]. Treatment selection is customized to the patient and depends on factors such as disease severity, lesion characteristics and location, as well as patient preferences[37]. It is important to understand that the perception of adequate control is partly a subjective issue.

In order to gain insight into the perception of long-term management of psoriasis in real clinical settings, this study focuses on the assessment of the biological agents (etanercept, infliximab, adalimumab, ustekinumab) in terms of efficacy and the longest drug survival. PASI score (Psoriasis Area and Severity Index) is the most common tool used by the clinicians to evaluate the extent and severity of psoriasis[38]. Secondary objective is to investigate whether the drug survival is associated with the anthropometric characteristics (gender, age, BMI) and the severity of the disease (baseline PASI score, duration of the disease, psoriatic arthritis, number of previous systematic treatments, concomitant treatment).

In the following chapters these issues are going to be addressed thoroughly. More specifically, the main findings of previous relevant studies will be presented in the Background chapter and the principles of Cox regression and Multiple Imputations will be addressed in the Statistical Methods section. The chapter of Methods-Data includes detailed description of the data collection process for this study, the variables, exposures and outcomes that will be used and the methods for handling each step of the analysis. Subsequently, the Results are going to be presented, naturally followed by the Discussion chapter, which involves interpretation of the results, comparison with previous studies, strengths and limitations of this study.

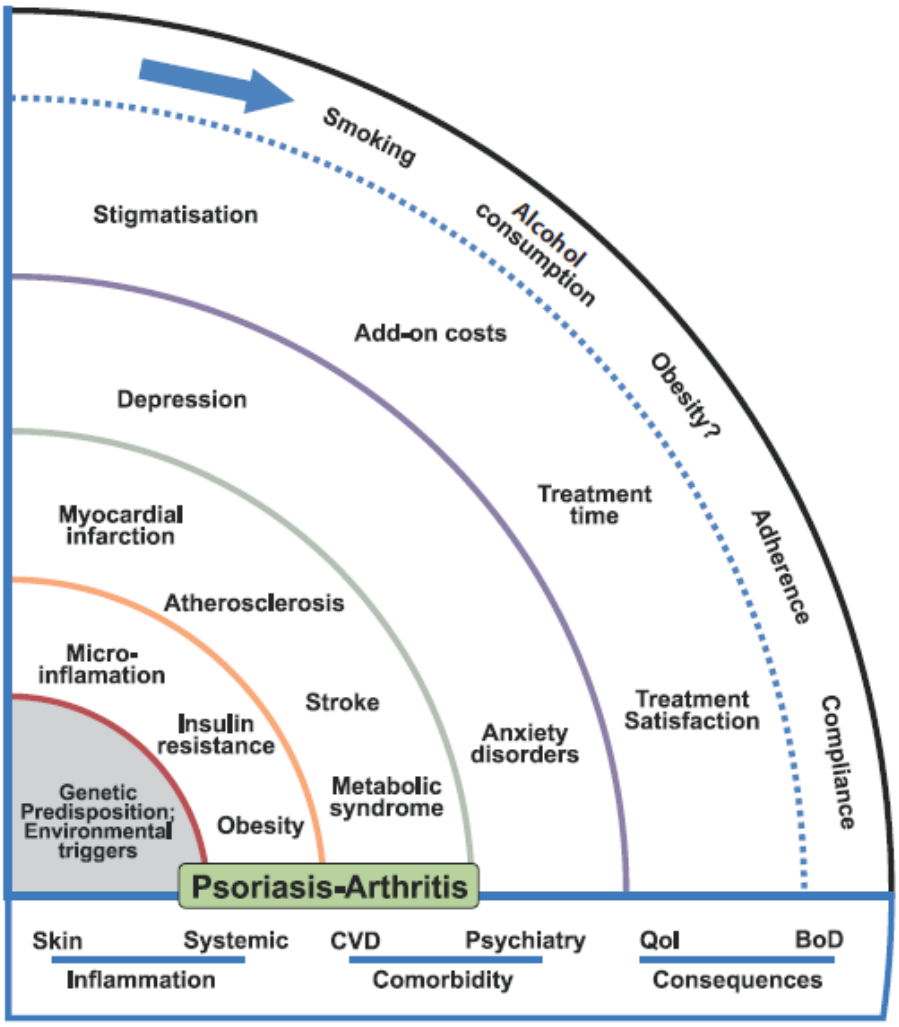



**Figure 1** : Integrated image of psoriasis as a chronic disease.
(Reference[39]: Mrowietz et al. 2014)

# Chapter 1: Background

According to the Global Report on Psoriasis, published by World Health Organization in 2016, many psoriatic patients have reported frustration with the ineffectiveness of their current treatment, expressing a persistent unmet medical need, as no long-term solutions are available for most patients[40]. Therefore, investigation of the drugs that meet the expectations of patients suffering from this chronic disease that requires long-term therapy to maintain clinical response has gained a lot of attention in the research community during the last decade.

The increased understanding of the immunopathology of psoriasis, combined with the great advance in the field of biotechnology has promoted the rapid development of biologic agents, genetically engineered proteins derived from living cells in the laboratory that target precisely parts of the immune system that fuel inflammation. Biologic agents were introduced for the treatment of plaque psoriasis in 2004, when etanercept[41], the first anti-TNF (Tumor Necrosis Factor) drug, got approval (European Agency for the Evaluation of Medicines Agency-EMEA). This is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor (TNFR) linked to the Fc fragment of human immunoglobulin IgG1. Infliximab[42] is an anti-TNF-a chimeric IgG1-monoclonal antibody composed of human constant and murine variable regions. Since it is administrated as intravenous (IV) infusion, infliximab requires monitoring by a physician or health-care provider and may provoke infusion reactions such as fever, chills, chest pain, low blood pressure or high blood pressure, shortness of breath, rash or itching. Adalimumab[43] is a recombinant human IgG1 monoclonal antibody specific for human TNF. Ustekinumab[44], the most new biological drug for plaque psoriasis-was approved in 2009, is a human IgG1 monoclonal antibody against the p40 subunit of the IL-12 and IL23 cytokines, produced through DNA recombinant technology.

As far as the therapeutic mechanisms of the above mentioned biologic agents are concerned, etanercept inhibits soluble TNF-a and TNF-b, whereas infliximab and adalimumab inhibit soluble and transmembrane TNF-a. Unlike the anti-TNF-a biologic agents (etanercept, infliximab, adalimumab) which target the TNF key-proinflammatory cytokine, ustekinumab influences the TH1 and TH17 immune pathways[45]. Interaction of activated T cells with monocytes/macrophages is mediated by the Th17/IL-23 axis[46] and plays a crucial role in maintaining the chronic inflammation in psoriasis.

An essential perspective of our study is that the patients suffering from psoriasis are bio-naive, that is they are treated with a biologic agent for the first time. The importance of this criterion relies on the fact that anti-drug antibodies (ADA) have been linked to decreased treatment efficacy with infliximab and adalimumab but not with etanercept[47]. Etanercept has the lowest percentage in the development of autoantibodies[48] (5%). The effect of anti-ustekinumab antibodies on treatment response is yet to be determined[49], although one study has reported a significant association between the presence of ADA and treatment failure[50]. It has been reported[51] that this undesirable immune response or immunogenicity may be associated with low drug levels just before the next dose, reduced clinical efficacy, shorter drug survival and an increased risk for adverse events, such as infusion reactions with infliximab.

In order to confront these potential problems clinicians have adopted several strategies for the reduction of ADA development, like intermittent therapy, personal dose adjustment or the concurrent administration of immunomodulators with biologics. However, the investigation on risk factors for ADA formation in psoriasis and the effect of concomitant immunosuppressive therapy, such as MTX (methotrexate)[52], as well as the optimal timing of administration[53], needs further exploration. In the era of personalized medicine pharmacogenetic studies[54] can cover many of these research gaps. The safety profile of MTX for each patient separately should be taken under serious consideration, since MTX is associated with elevated liver enzyme levels[55], but can be recommended when a significant joint damage exists.

Primarily, our study focuses on the calculation and comparison of the drug survival among etanercept, infliximab, adalimumab and ustekinumab. Since there is only scarce evidence about the cross-reaction potential of ADA for multiple TNF antagonists in psoriasis[56], we are including only bio-naive patients and underline the importance of drug survival. Measuring the drug levels just before the next dose and testing for ADA when the dilemma of switching biologic agent is apparent, could be a valuable tool in the decision process[57]. It is suggested, in a similar perception, that the subgroup of

non-responders without anti-TNF ADA started treatment based on a non-anti-TNF mechanism of action for patients with rheumatoid arthritis[58]. Switching to another biologic agent involves a higher cost[59], perhaps the cost of an induction regimen which is significantly higher than a maintenance regimen.

During the last decade several studies have been conducted focusing on the drug survival explicitly (Table 3) or in addition to the assessment of the efficacy of biologic agents used in psoriasis therapy . When only anti-TNF-α biologics were examined[60], etanercept was reported with the longest drug survival (51.4 months), followed by infliximab (36.8 months) and adalimumab (34.7 months). The longer drug survival of etanercept in comparison to infliximab was also identified in a systematic review[61] of 19 clinical trials. Another multi-centre study[62] concluded that etanercept (47.9 months) and adalimumab (42.1 months) were superior to infliximab (15.9 months) as far as the drug survival is concerned. On the other side, a study[63] analyzing the Danish DERMBIO registry demonstrated longer drug survival of infliximab, followed by adalimumab and etanercept. One study[64] demonstrated that drug survival did not differ significantly for bio-naive patients among the 3 anti-TNF biologics, as etanercept decreased from 85% to 64% at year 1–4, while adalimumab and infliximab drug survival at year one was77% and 75% respectively and remained stable until at least year four.

More recent studies include also ustekinumab, the newest among the 4 biologic agents that we involve in our study. One large international prospective study[65] showed that among the bio-naive psoriatic patients the median drug survival was superior for ustekinumab (10.5 months) than infliximab (10.2 months), adalimumab (8.6 months) and etanercept (7.2 months). A long-term prospective study[66] reinforced the better drug survival of ustekinumab than adalimumab and etanercept. An important remark is that a long-term study[67] proved that ustekinumab lost its advantage in drug survival over adalimumab and infliximab, but maintained it over etanercept, when the group of non bio-naive patients was examined. One study[68] designed to include only bio-naive psoriatic patients concluded that the first year survival rate for ustekinumab was 89%, adalimumab 79%, etanercept 70% and infliximab 65%. Moreover, ustekinumab presented the longest drug survival in several smaller studies[69,70].

The secondary objective of our study, as mentioned above, is the assessment of the efficacy of the biologic agents etanercept, infliximab, adalimumab and ustekinumab. Although the drug survival may reflect partially the personal perception and satisfaction of the psoriatic patient for the biologic modality, the use of a widely accepted tool by the physician in order to measure the efficacy of the drug is a necessary complement. For this purpose, PASI (Psoriasis Area and Severity Index) is a quantitative scoring system[36] that combines assessment of the extent of the involved area(A) with the severity of the signs of erythema(E), desquamation(D) (scaling) and induration(I) (lesion thickness) on a scale of 0-4 (none to very severe) at each of four body regions: upper(U) and lower(L) extremities, trunk(T) and head(H). The percentage of involvement of the four anatomical regions is assigned a numerical value of 0–6 with 0 indicating no involvement, 1 = 1–9%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89% and 6 = 90–100%. For the final calculation of PASI, the 4 anatomical regions are evaluated according to their proportion of the whole skin and the cumulative score is the result. The formula is: PASI=0,1 (EH + IH+DH) AH+ 0.3 (ET + IT+DT) AT +0.2 (EU+ IU +DU) AU + 0.4 (EL + IL+DL) AL. The range of PASI score is 0-72, with 0 meaning no lesions[71,72]. Moderate or severe psoriasis is defined as PASI score over 10, while PASI50, PASI75 and PASI90 represent the dynamic parameters for the proportion of patients who reach as improvement of 50%, 75% and 90% of the baseline score after receiving treatment. When someone has achieves PASI100, it reflects the totally clean condition[73]. Mean PASI is useful for the interpretation of the kinetics, the velocity of the onset of response.

When a biological treatment is prescribed, the PASI score is used from the dermatologists in order to consider the start, the maintenance or the switching. The latter is an alternative if an adequate response is not reached, defined as either a PASI 75 or a PASI 50 and a 5-point reduction in DLQI (Dermatology Life Quality Index, refers to the last week) from the start of treatment. The time point of assessing a primary failure differs according to the biologic drug: 10 weeks after starting treatment for infliximab, 12 weeks for etanercept, and 16 weeks for adalimumab and ustekinumab. Discontinuation of a biologic agent is also considered if the psoriasis initially responds adequately but subsequently loses this response (secondary failure) or the first biological drug cannot be tolerated or becomes contraindicated. It is worth mentioning that indication of infliximab requires[74] a condition of very severe psoriasis as defined by a total PASI of 20 or more and a DLQI of more than 18.

Interestingly, recent studies[75] support the association between a significant improvement in PASI score and an improvement in the health-related quality of life of affected patients.

Several studies have investigated the efficacy of biologic agents in the treatment of moderate-to-severe psoriasis (Table 2). One meta-analysis[76] of clinical trial results has concluded that when efficacy was assessed at the primary endpoint times (infliximab: week 10, etanercept: week 12, ustekinumab: week 12, adalimumab: week 16) inflixmab had the greatest probability of response with respect to placebo for PASI50, PASI75 and PASI90. Efficacy assessed by PASI75 in comparison with the placebo group was greater for infliximab (RD: Risk Difference=75.7%, 95%CI: 72.1-79.3%), followed by ustekinumab 45mg (RD 70.1%, 65.8–74.3%), ustekinumab 90mg (RD 66.5%, 60.2–72.9%), adalimumab (RD 63.0%, 59.3–66.7%), etanercept 50 mg biweekly (RD 43.5%, 40.0–47.1%) and etanercept 25mg biweekly or 50mg weekly (at week 12) (RD 31.0%, 26.6–35.4%). However, when the analysis examined the timepoints approved by SmPCs (recommendations in the Summaries of Product Characteristics) (etanercept: week 12, adalimumab: week 16, infliximab: week 14-22, ustekinumab: week 28) ustekinumab 45mg has the greatest probability of achieving PASI50 response (RD 80.7%, 77.2–84.2%), followed by ustekinumab 90 mg, infliximab, adalimumab and etanercept. The same order is apparent at the end of the induction phase (week 24), with ustekinumab 45 mg having the greatest probability of achieving PASI75 response (RD 75.5%, 71.5–79.4%). Another meta-analysis[77] reported similar results for a higher probability to achieve PASI90 response compared to placebo at week 24-28 with ustekinumab (RR: Relative Risk=31.63, 95%CI: 19.43,51.51, $I^2$=0%), infliximab (RR 31.00, 95%CI: 13.45,71.46, $I^2$=0%), adalimumab (RR 23.17, 95%CI: 12.51,42.91, $I^2$=0%) and etanercept (RR 19.14, 95%CI: 11.59,31.60, $I^2$=0%).

In daily clinical practice, one study demonstrated that among anti-TNF-α factors, infliximab scored the best for both PASI75 and PASI90 (69.8% and 50.9% respectively), followed by adalimumab (65% and 35.7%) and etanercept (49.7% and 21.2%) at 4 months. Another highlight from this study is that survival rates correlated significantly with effectiveness for adalimumab and etanercept, but not for infliximab[62]. Taking under consideration the importance of maintaining the good response to one biologic agent, one study showed that in the bio-naive group of patients adalimumab achieved the greatest a PASI90 response both at weeks 12 and 52 (42.9% and 43.5% respectively), followed by etanercept (9.9% and 13.3% ) and infliximab (35.3% and 18.2%)[64]. A small study examining the one-year PASI75 response reported that infliximab outperformed ustekinumab and adalimumab[69]. One study underlined that achieving PASI75 or PASI90 response at the end of the induction period (16 weeks) is a positive predictor of drug survival[70].

Reasons for discontinuation as well as factors predicting the drug survival of biologic agents are important factors that have been explored in a few studies.

At this point we need to mention that several adverse events have occurred rarely to patients using biological agents. The most serious include hypersensitivity to the biological agent, congestive heart failure; sepsis, tuberculosis, hepatitis B and demyelinating disorders[78].

All in all, what is important to notice is that biological therapies represent both a challenge and a promise of a more peaceful future for the psoriatic patients[79].

| | Etanercept (ETN) | Infliximab (INF) | Adalimumab (ADL) | Ustekinumab (UST) |
|---|---|---|---|---|
| **mechanism of action** | anti-TNF-α | anti -TNF-α | anti -TNF-α | anti -IL12/23 |
| **administration** | subcutaneous injection (SC) | intravenous injection (IV) | subcutaneous injection (SC) | subcutaneous injection (SC) |
| **dosage (FDA)** | for 3 months: 50mg 2x wks.<br>then : 50mg 1x wk. | 0, 2 and 6 wks.: 5mg/kg<br>then every 8 wks.: 5mg/kg | initial dose: 80mg<br>1wk after & then every 2nd wk.: 40 mg | weight < 100 kg<br>initial dose: 45mg<br>4 wks. later & then every 12 wks: 45 mg<br>weight > 100 kg<br>initial dose: 90mg<br>4 wks. later & then every 12 wks: 90 mg |

**Table 1**: Basic characteristics of etanercept, infliximab, adalimumab and ustekinumab

| Study | Biol. agents | Design | Results |
|---|---|---|---|
| Puig et al (2014) | ETN, INF, ADL, UST | meta-analysis of clinical trials | primary endpoint :<br>PASI75 vs placebo: INF> UST> ADL> ETN<br>drug instructions:<br>PASI50 vs placebo: UST> INF> ADL> ETN<br>end of induction week (24th wk. ) :<br>PASI75 vs placebo: UST> INF> ADL> ETN |
| Nast et al (2015) | ETN, INF, ADL, UST | meta-analysis of clinical trials | PASI90 vs placebo , 24-28th wk.:<br>UST > INF > ADL > ETN |
| Umezawa et al (2013) | INF, ADL, UST | prospective, small single-centre, observational (Japan) | 1 year , PASI-75 :<br>INF (68.4%) > UST(63.3%) > ADL(50.8%) |
| Menting et al (2014) | ETN, INF, ADL | single-centre, observational (Netherlands) | 1st treatment, PASI90, 12th \| 52nd wk. :<br>ADL (42.9\|43.5%) ><br>> ETN (9.9\|13.3%) > INF (35.3\|18.2%) |
| Inzinger et al (2016) | ETN, INF, ADL | Psoriasis Registry (Austria) | PAI75 \| PASI90 , 4 mon. :<br>INF (69.8\|50.9%) ><br>> ADL (65\|35.7%) > ETN (49.7\|21.2%) |

**Table 2**: Studies on efficacy of biologic agents in the treatment of moderate-to-severe psoriasis

| Study | Biol. agents | Design | Results |
|---|---|---|---|
| Noiles et al (2009) | ETN, INF | systematic review of 19 clinical trials | ETN > INF |
| Gniadecki et al (2011) | ETN, INF, ADL | DERMBIO registry (Denmark) | 4-year drug survival :<br>INF (70%) > ADL (40%) ~ ETN (40%) |
| Esposito et al (2013) | ETN, INF, ADL | multi-centric, observational (Italy) | ETN(51.4 mon.)> INF(36.8) > ADL(34.7) |
| Menting et al (2014) | ETN, INF, ADL | multi-centric, observational (Netherlands) | no stat. sign. difference in 1st treatment (1\|4 yrs):<br>ETN(85\|64%), ADL(77\|77%), INF (75\|75%) |
| Inzinger et al (2016) | ETN, INF, ADL | Psoriasis Registry (Austria) | ETN(47.9 mon.)> ADL(42.1)> INF(15.9) |
| Gniadecki et al (2014) | ETN, INF, ADL, UST | DERMBIO registry (Denmark) | 1st treatment :<br>UST~ ADL, INF \| but remains UST>ETN |
| Warren et al (2015) | ETN, INF, ADL, UST | prospective, BADBIR Registry (UK) | 1st treatment, 1 year :<br>UST(89%)>ADL(79%)>ETN(70%)>INF(65%) |
| Menter et al (2016) | ETN, INF, ADL, UST | multi-centric , observational international (PSOLAR) | 1st treatment :<br>UST (10.5 μήνες) ><br>> INF (10.2) > ADL (8.6) > ETN (7.2 ) |
| Zweegers et al (2016) | ETN, ADL, UST | prospective BioCAPTURE Registry (EU) | 1 year :<br>UST (84%)> ETN (75.8%)> ADL (74.6%)<br>5 yrs :<br>UST (61% )> ADL (41%) and ETN(34%) |

**Table 3**: Studies on the drug survival of biologic agents in the treatment of moderate-to-severe psoriasis

# Chapter 3: Statistical Methods

## 3.1 : Cox Regression

Survival analysis is the statistical approach used commonly, especially in medical research, for the modeling of the time until an event occurs ("time-to-event"). The main feature of survival data that renders standard methods inappropriate is that survival times are frequently censored. This occasion occurs when the end-point of interest (event) has not been observed for an individual, either because the study ended before the event took place or because the subject is "lost to follow up" with an unknown survival status at the time of the analysis[80].

The Cox proportional-hazards regression model (Cox PH model), introduced by Cox in 1972[81], is the most widely used method for the modeling of the relationship between survival and one or more possible covariates. It is a semi-parametric model, as there is no assumption required for the baseline hazard distribution, integrating the advantages of nonparametric and parametric approaches in order to serve the analysis of survival data[82].

The formula describing how the Cox PH model relates covariates to the hazard function is[83]:

$$h(t|x) = h_0(t)c(\beta' x)$$

where :

- $h_0(t)$ : the baseline hazard function
  (hazard function for an individual for whom all the variables included in the model have 0 value)
- $\beta'=(\beta_1,\beta_2 \dots \dots \beta_p)$ : a parameter vector of regression coefficients
- $x=(x_1,x_2 \dots \dots x_p)'$ : the value of the vector of explanatory variables for a particular individual
- $c(\cdot)$ : a fixed, known scalar function
- $h(t|x)$ : the hazard function (at time t given x)

The baseline hazard function $h_0(t)$ is the non-parametrical component of the model, while the covariate effect $c(\beta' x)$ is the parametric component, with the covariates entering the model linearly :

$$c(\beta' x) = e^{(\beta' x)} = e^{\left(\sum_{j=1}^{p} \beta_j x_{ji}\right)}$$

Proportional hazards :
The Cox model is called a proportional hazards model since the ratio of hazard rates of two individuals with covariate values $x_1$ and $x_2$, at time t, is independent of t :

$$\frac{h(t|x_1)}{h(t|x_2)} = \frac{h_0(t)e^{(\beta' x_1)}}{h_0(t)e^{(\beta' x_2)}} = \frac{e^{(\beta' x_1)}}{e^{(\beta' x_2)}} = e^{\left[\beta'(x_1 - x_2)\right]}$$

Hazard function at time t given covariate x : $h(t|x) = h_0(t)e^{(\beta' x)}$

Cumulative hazard function : $H(t|x) = \int_0^t h(u \mid x)du = \int_0^t h_0(u)e^{(\beta' x)}du = H_0(t)e^{(\beta' x}$

Survival function : $S(t|x) = e^{-[H(t \mid x)]} = e^{-\left[H_0(t)e^{(\beta' x)}\right]}$

Probability density function : $f(t|x) = h_0(t)e^{(\beta' x)}\, e^{-\left[H_0(t)e^{(\beta' x)}\right]}$

For the estimation of the regression parameters, the partial likelihood function has been proposed by Cox[81] which depends only on β :

$$L(\beta) = \prod_{i=1}^{n} \left[\frac{e^{(\beta' x_i)}}{\sum_{k \in R(t_i)} e^{(\beta' x_k)}}\right]^{\delta_i}$$

where :

- $R(t_i)$ : the risk set at time $t_i$
- $\delta_i$ : the event indicator ($i^{th}$ survival time is right censored=0, $i^{th}$ survival time is event=1)

The partial likelihood is valid when there are no ties in the dataset.

Checking the Proportional Hazards assumption :
As the assumption of proportional hazards is the basic idea of the Cox PH, there are several methods for the verification of this quality of the model.

The graphic method examines the proportionality of hazards by plotting the estimated *-log(-log(survival))* versus survival time for 2 groups. If the assumption is true, the lines would be parallel. This method cannot have clear results when there are categorical variables with many levels[84].

The scaled Scoenfeld residuals method is testing the lack of proportionality, with null hypothesis being a constant function over time :

$$r^*_{pji} = (V^{-1})r_{pji}$$

where :

- $r^*_{pji}$ : scaled Schoenfeld residual
- $(V^{-1})r_{pji}$ : inverse of the estimated variance-covariance matrix of the Schoenfeld residual

If the proportional hazards assumption is true, a straight horizontal line with zero slope is expected at the relevant plot[85,86].

The Cox PH model can be expressed in the following form :

$$\log\left\{\frac{h_i(t)}{h_0(t)}\right\} = \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}$$

Therefore, it can be regarded as a linear model for the logarithm of the hazard ratio[80].

## 3.2 : Multiple Imputations

Missing data is a common problem in medical and epidemiological research. When many missing values are present in the dataset, instead of excluding the records from the analysis and taking the risk of losing power of the estimation, the method of multiple imputations can be used.

The multiple imputation method, as presented by Rubin in 1987, replaces each missing value by two or more plausible values, or in an algebraic framework, by a vector composed of m≥2 possible values. The first components of the vectors for the missing values are used to create one complete dataset, the second components of the vectors are used to create the second complete dataset and so on. Afterwards, each complete m dataset is analyzed through standard complete-data methods[87]. Finally, the pooling step integrates the m results into a final result by computing the man over the m analyses, its variance and its confidence interval or p-value[88].

An important notion in the context of multiple imputations is the examination of the nature of the missingness of the data. When data are missing completely at random (MCAR), the probability of missingness is not related either to the observed data or to the unobserved (missing) data. As a result, there is no selection effect due to missingness and the observed data are representative for the missing with respect to all relevant variables. In fact, MCAR is an optimal sub-category of missing at random (MAR) data pattern. In this occasion the probability of missingness may be related to the observed data, but not to the unobserved. The missing data can be predicted accurately by the observed values. On the other side, for data missing not at random (MNAR) the probability of missingness is related to missing data values as well[89].

Examining whether the data are MCAR can be performed by using Little's test[90]. This is a Wald-type Chi-square statistic ($X_1^2$), with null hypothesis that missingness is MCAR. The method is based on dividing respondents into those with and without missing data and testing if the variables in these 2 groups differ significantly. An insignificant p-value of Little's test is interpreted as enabling the MCAR assumption[91,92]. The Troxel's index of sensitivilty to non-ingorability (ISNI) is a useful tool for the assessment of the random distribution (ignorable) across observations. For this purpose, a non-ignorability parameter measures the extent of the dependence of the probability of a given observation upon the available data, including missing values. ISNI is the extent to which an estimate of this regression coefficient, for a given non-ignorability parameter, depends on possible values for this parameter. A zero value of this parameter is translated as the verification of MAR missing values[90,93,94].

In the present study, the MICE method (multiple imputation by chained equation) will be used for the performance of analyses based on complete datasets. The MAR condition for the missingness pattern needs to be satisfied for accurate results in this method. A chain of regression models is used for the imputation of missing values of two or more variables. As described above, the missing values of one variable are imputed given the observed values of other variables, then the missing values of second variable are imputed given the imputed variable and observed values of other variables and so on until all the missing values are replaced. Briefly explained, each iteration is using one variable as an outcome and the remaining variables as predictors. If the outcome has any missing values, the predicted values from the regression are imputed. Iterations end when all variables in the dataframe have served as an outcome.

The fundamental advantage of this technique is its flexibility in handling different types of variables, binary, categorical and continuous. Let **X** ($X_1, X_2, \ldots, X_k$) be the vector of variables with missing values and **Z** ($Z_1, Z_2, \ldots, Z_l$) be the vector of variables with all the values observed. Initially, missing values of all variables are filled in at random from observed values of corresponding variables. The first variable with missing values, $X_1$, is regressed on the other variables $X_2, \ldots, X_k$ and **Z,** restricted to individuals with observed $X_1$ values. The parameter coefficient of this regression, say $\vartheta$, is replaced by $\vartheta *$ obtained from simulated draws from its posterior distribution. Missing values in $X_1$ are replaced by the values generated by fitting regression models. Then, $X_2$ is regressed on $X_3, \ldots, X_k$, **Z** and imputed $X_1$, with records restricted to observed $X_2$ values. Again, missing values in $X_2$ are replaced by draws from the posterior predictive distribution of $X_2$. The process is iterated until all other variables with missing values have been updated. The whole process (cycle) runs several times in order to find the

convergent values of parameters[95]. According to the literature usually 10 cycles are adequate[96,97]. The entire procedure is repeated independently m times, producing m imputed datasets.

# Chapter 4: Materials and Methods

## 4.1 : Data collection

The data for this study were collected from the medical records of patients (paper files or electronic records). For 25 out of 134 patients additional information on the relevant medical history was extracted via telephone calls, due to excessive missingness. The collection procedure was conducted from 1-4-2015 to 20-5-2016 (date of data lock).

## 4.2 : Study design - Settings - Participants

The design of this study is a single-centre, observational prospective study with partially retrospective data collection. This centre is "Attikon" Tertiary General University Hospital-Psoriasis outpatient clinic, in Athens, Greece. Period of inclusion of the participants was from 2004 to 2016 (more specifically from 15-5-2004 to 13-1-2016). The study population includes 134 psoriatic patients with first-time treatment with biological agent. Therefore, any previous treatment with anti-TNFα and/or antiIL-12/23 agents is considered the exclusion criterion.

## 4.3 : Exposures - Outcomes - Variables

Exposures :
The biological agent is defined as the exposure in the study analysis. In detail, the population consists of 58 patients using etanercept, 21 patients using infliximab, 30 patients using adalimumab and 25 patients using ustekinumab.

Outcomes :
There are two main outcomes measured, in order to serve the objectives of the study, as they are explained in the Introduction Chapter. Firstly, the drug survival is measured in weeks and expresses the time to discontinuation of the first biologic agent. Here it used as a composite outcome, including all 3 causes of discontinuation: lack of effectiveness or loss of response, adverse event and patient's choice or insurance reasons. Cases which are lost to follow-up or continue the same treatment are censored. Secondary outcome is the response of the psoriatic patients to the therapy after one year of treatment. More specifically, measurements were conducted in the $52^{nd}$ week of treatment, with a window of 40-64 weeks being accepted, based on one similar approach[62]. Although PASI50, PASI75 and PASI90 are presented, only PASI75 was selected as an outcome reflecting the adequate level of response, in line with the current clinical guidelines, for the percentage in change of measured PASI from the baseline PASI score.

Variables :
In order to assess whether the drug survival is associated with the anthropometric characteristics and the severity of the disease several variables were identified or measured. Both age at the onset of treatment, age at the onset of psoriasis in years and gender are recorded. BMI ($kg/m^2$), weight (kg) and waist circumference (cm) are used. Family history of psoriasis, current smoking and alcohol current use are also part of the medical history as bivariate variables. The baseline PASI, duration of psoriasis (years), present scalp lesions, present nails' lesions until the start of the first-time biological treatment and type of psoriasis are measured. Moreover, we assess important comorbidities (psoriatic arthritis, hypertension, diabetes, dyslipidemia, coronary heart disease) and any concomitant treatment (none, methotrexate-MTX, cyclosporine-CyA or retinoids) as present or not. The number of previous systematic treatments (0-3: among MTX, CyA and retinoids) is a categorical variable, while the duration of treatment (in weeks) and the status of the patient at the end of the study (continues, discontinues or is lost to follow up) are essential variables for the drug survival analysis. Start of the biological treatment during-after 2009 or before 2009 is included as a variable for adjustment as from the beginning of that year all 4 drugs were on the Greek market.

## 4.4 : Statistical Analysis

For the part of the statistical analysis, the R programming language is used in the study (R version 3.2.3, 2015-12-10)[98].

### 4.4.1 Baseline descriptive statistics of the study population

The baseline descriptive statistics of the study population are presented in tabular form. Except for the frequency as percentage, numbers in brackets are also used to describe the ratio numbers of individuals/number of individuals with data available. Variables with a Gaussian distribution are presented as mean ± SD (standard deviation), whereas non-parametrically distributed variables are presented as median [IQR] (interquartile range).

The exploration of difference between the 4 treatments is conducted with the use of Fisher's exact $X^2$ test for categorical variables, one-way ANOVA for continuous variables with parametric distribution and Kruscal-Wallis for continuous variables with non-parametric distribution.

A short exploratory analysis follows, concerning the potential effect of combining the separate components of metabolic syndrome on the difference among the 4 treatments. The categorization of BMI according to WHO is also examined in the same context.

### 4.4.2 Linear Interpolation for missing data

We realized during the data collection and verified during the data preparation with the use of statistical program that the percentage of missing values was too high for the PASI at the last known date.

| **Percentage of Missing values per variable** | |
|---|---|
| Concomitant treatment | 1.49% |
| Duration of treatment (weeks) | 9.7% |
| Baseline PASI | **28.36%** |
| PASI50, PASI75, PASI90 at last known date | **55.22%** |
| Number of previous systemic treatments | 16.42% |
| Type of psoriasis | 12.69% |
| Psoriatic arthritis | 9.7% |
| Scalp lesions | 7.46% |
| Nails lesions | 7.46% |
| Family history | 15.67% |
| Weight | 9.7% |
| BMI | 12.69% |
| Waist circumference | 52.99% |
| Smoke use | 13.43% |
| Alcohol use | 15.67% |
| Hypertension | 5.97% |
| Diabetes mellitus II | 4.48% |
| Dyslipidemia | 5.97% |
| Coronary Heart Disease | 14.93% |
| Age at onset of treatment | 4.48% |
| Disease Duration (yrs) | 7.46% |
| Comorbidity | 8.96% |
| Metabolic component | 8.96% |
| Start during/after or before 2009 | 2.99% |

**Table 4:** Percentage of missing values per variable in our study sample

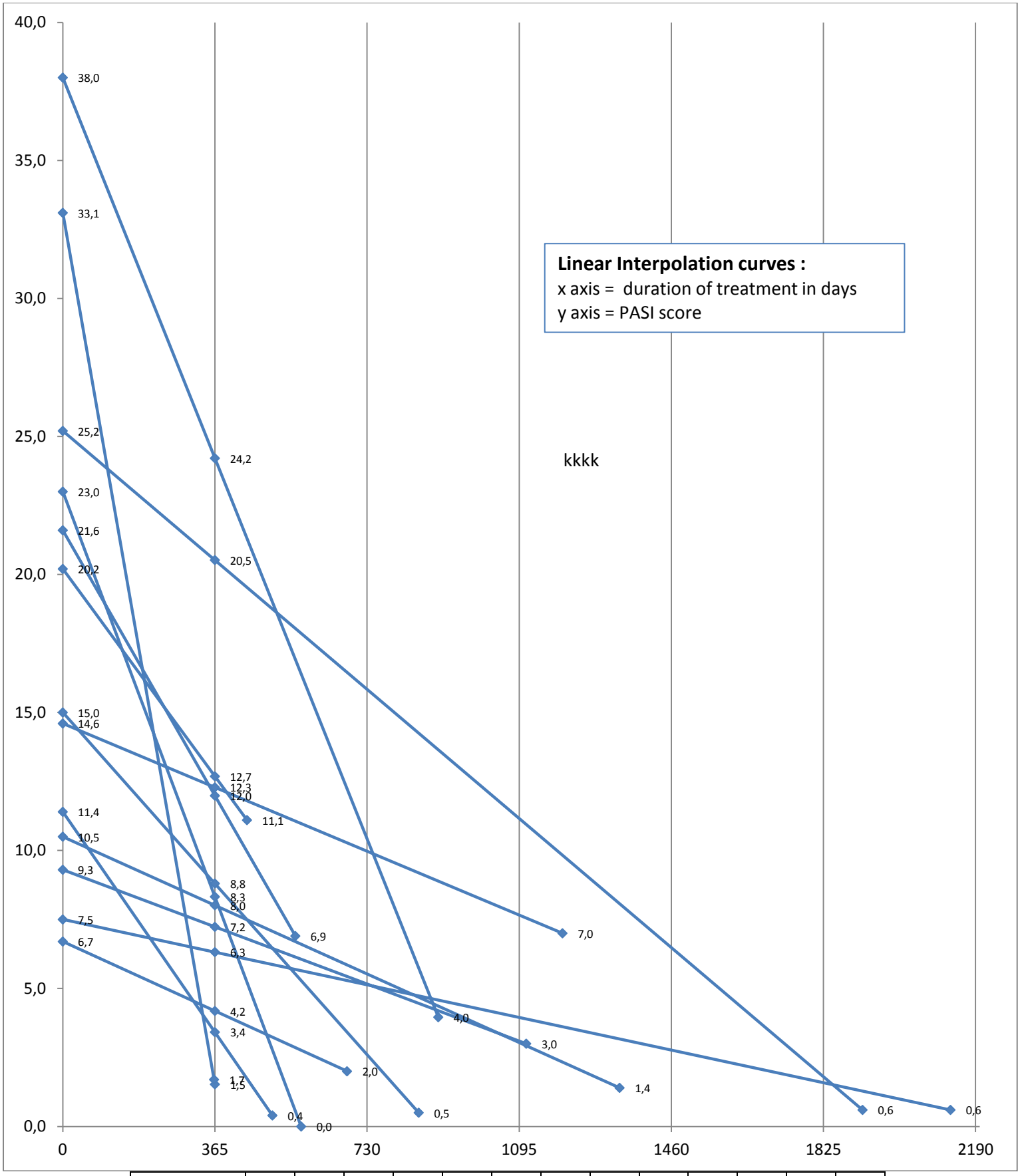
One goal of this study is the comparison of the efficacy among the 4 biological agents through the measurement of the PASI score at the 1st year (52 week) of treatment (window: 44-60 weeks). PASI50, PASI75 and PASI90 are the final outcomes. 12 patients had these data available for this specific time period.

For the handling of missing data, a subset of 20 other patients who had available measurements of PASI score at 3 distinct dates was used. 4 of them had already their final measurement before the minimum window limit (day 308), so they were excluded from the analysis for the handling of missing data. Moreover, 3 out of the 20 patients were excluded from this analysis as they were in remission during the window period, so they would be difficult to handle.

As a result, 13 patients with 3 measurements of the PASI score were utilized in order to obtain their measurements in the 365th day of their treatment through the linear interpolation method[62]. They all had their 2nd measurement before the window of the 1st year. Therefore, the requested PASI score on the 365th day of treatment (table: Interpolated 365th) is located on the axis of time between the baseline PASI and the 2nd PASI measurement. In total, 12 + 13=25 patients can be used for the calculation of the PASI50, PASI75 and PASI90.

| ID | start_date | second_date | stop_date | Start PASI | Second PASI | Stop PASI | Interpolated 365th |
|---|---|---|---|---|---|---|---|
| **100** | 30/06/08 | 30/04/14 | 06/05/16 | 7,5 | 0,6 | 0 | 7,4 |
| **57** | 30/06/09 | 01/10/14 | 15/05/16 | 25,2 | 0,6 | 0 | 25,0 |
| **7** | 15/07/10 | 12/03/14 | 10/08/15 | 10,5 | 1,4 | 0 | 10,4 |
| **81** | 30/06/07 | 11/10/10 | 15/05/16 | 14,6 | 7 | 0,6 | 14,5 |
| **128** | 01/08/12 | 18/08/15 | 06/05/16 | 9,3 | 3 | 0 | 9,2 |
| **110** | 30/06/10 | 17/12/12 | 15/05/16 | 38 | 3,96 | 1,2 | 37,7 |
| **65** | 15/06/10 | 16/10/12 | 15/01/14 | 15 | 0,5 | 9,8 | 14,9 |
| **112** | 24/11/08 | 07/10/10 | 03/02/12 | 6,7 | 2 | 6,4 | 6,7 |
| **33** | 14/12/12 | 09/07/14 | 06/05/16 | 23 | 0 | 3,9 | 22,8 |
| **50** | 15/03/13 | 24/09/14 | 15/05/16 | 21,6 | 6,9 | 9,4 | 21,5 |
| **5** | 16/05/13 | 01/10/14 | 15/04/16 | 11,4 | 0,4 | 0 | 11,3 |
| **45** | 30/06/11 | 14/09/12 | 15/12/12 | 20,2 | 11,1 | 7,6 | 20,1 |
| **87** | 29/11/11 | 26/11/12 | 06/05/16 | 33,1 | 1,7 | 0 | 32,8 |

**Table 5 :** Data of the group of patients after linear interpolation




| ID | 100 | 57 | 7 | 81 | 128 | 110 | 65 | 112 | 33 | 50 | 5 | 45 | 87 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Start PASI | 7,5 | 25,2 | 10,5 | 14,6 | 9,3 | 38 | 15 | 6,7 | 23 | 21,6 | 11,4 | 20,2 | 33,1 |

**Figure 2 :** Visualization of the data of the group of patients after linear interpolation

### 4.4.2 Drug survival models with confounder correction

The classic visual representation of drug survival models in Kaplan-Meier curves was used. Moreover, log-rank test were performed in order to determine any statistically significant important difference in drug survival of the 4 biological agents. An additional stratified log-rank test was performed including any significant baseline categorical variable from the analysis above together with gender and age at the onset of treatment, which are fixed variables.

### 4.4.3 Cox Regression analysis for Drug Survival

The statistical analysis for the estimation of the hazard ratios of discontinuating the biological agent was conducted with Cox Regression models (Chapter 3.1 for the mathematical theory behind these models). We took under consideration controlling for the following possible confounders: gender, age at onset of treatment, BMI as a categorical variable (according to the 5 WHO categories) and initiation of treatment during/after 2009 or before (since in 2009 all 4 biological agents were available in the market). The selection of these variables was made with relevant previous studies as a basis (see Chapter 2).

### 4.4.4 Multivariate Cox Regression analysis for possible Predictors

Covariates were examined in Cox Regression models as predictors of time to discontinuation, when the treatment (biological agent) is forced in the initial model. These covariates have been examined in previous studies for the same purpose: gender, age at the onset of treatment, concomitant treatment, duration of psoriasis (years), baseline PASI, psoriatic arthritis, number of previous systematic treatments, BMI (according to the 5 WHO categories) and initiation of treatment during/after 2009 or before (since in 2009 all 4 biological agents were available in the market). The backward method for selection of the final model was used, with entry level put on p-value=0.2. The proportional hazard assumption is tested using Schoenfeld residuals. Results are presented as hazard ratios (HRs) with their corresponding 95% Confidence Intervals.

In addition, multiple imputation methods (Chapter 3.2 for the mathematical theory behind this method) are applied in order to force the baseline PASI as one essential variable in the model and check if there are any important differences from the complete cases analysis in the final models produced from the 2 Cox regression approaches. The mice package was used in R[99]. Little's test was performed to test the hypothesis of MCAR data. Moreover, it was inferred that the missing data were MAR as the source of missingness were the incomplete medical files[100,101]. We produced 10 multiple imputation datasets, in line with the recommendation of setting the number of multiple imputations to the average of missing data (for the above 9 variables, there is 8.46% average missing values)[102]. For the imputation of the missing data of the above 9 variables, the relevant method was used automatically: logistic regression for the categorical (concomitant treatment, BMI, number of previous systematic treatments) and binary (gender, psoriatic arthritis, initiation of treatment during/after 2009 or before) variables and linear regression for the continuous (age at the onset of treatment, duration of psoriasis, baseline PASI). The regression coefficients and standard errors were combined across imputed data sets using the Mitools package.

### 4.4.5 Subgroup analysis for psoriatic patients with psoriatic arthritis

As an interesting and common comorbidity occurring to psoriatic patients, psoriatic arthritis was examined with subgroup analysis. The relevant covariate and the interaction term with biological agent was added to the model produced through the multiple Cox Regression analysis.

# Chapter 5: Results

## 5.1 : Baseline descriptive statistics of the study population

| Psoriasis ATTIKON study (N=134) | | | | | | |
|---|---|---|---|---|---|---|
| **Patient Characteristics** | **Etanercept N=58** | **Ustekinumab N=25** | **Infliximab N=21** | **Adalimumab N=30** | **p-value** | **All subjects N=134** |
| Age (yrs), median [IQR] | 46.5 [34.5-58.5] n=54 | 50 [37.5-58.5] n=23 | 42 [34-48] n=21 | 48.5 [35.5-53] n=30 | 0.426¥ | 46 [34.8-56.3] n=128 |
| Age at onset of psoriasis (yrs), median [IQR] | 27 [20-41] n=57 | 35 [22.8-43.8] n=24 | 25 [17-27.8] n=18 | 29.5 [22.8-40.8] n=28 | 0.331¥ | 27 [20-40.5] n=127 |
| Male gender, % (no) | 55.2 (32/58) | 68 (17/25) | 52.4 (11/21) | 66.7 (20/30) | 0.511‡ | 59.7 (80/134) |
| BMI($kg/m^2$), median [IQR] | 28.7 [27-32.3] n= 52 | 28.4 [25.8-31.4] n=18 | 30.4 [24.2-37] n=19 | 28.4 [23.4-30.4] n=28 | 0.675¥ | 28.5 [26-32.2] n=117 |
| Central obesity, % (no) (BMI>30$kg/m^2$) | 36.5 (19/52) | 33.2 (6/18) | 52.6 (10/19) | 28.6 (8/28) | 0.416‡ | 36.8 (43/117) |
| Weight, median [IQR] | 84.5 [73.3-93] n=54 | 92.5 [79.5-99.8] n=18 | 87.5 [72.5-102.3] n=20 | 84 [71-95] n=29 | 0.658¥ | 85 [74-99] n=121 |
| Waist circumference, mean (SD) | 108 (12.43) n=22 | 101.9 (12.88) n=14 | 101.5 (14.96) n=10 | 103.1 (16.79) n=17 | 0.489† | 104.3 (14.16) n=63 |
| Family history, % (no) | 27.5 (14/51) | 28.6 (6/21) | 33.3 (6/18) | 43.5 (10/23) | 0.575‡ | 31.9 (36/113) |
| Smoke current use, % (no) | 64.7 (33/51) | 66.7 (14/21) | 55.6 (10/18) | 61.5 (16/26) | 0.884‡ | 62.9 (73/116) |
| Alcohol current use, % (no) | 24.5 (12/49) | 19 (4/21) | 16.7 (3/18) | 32 (8/25) | 0.669‡ | 23.9 (27/113) |

*numbers in brackets : numbers of individuals/number of individuals with data available,*
*Variables with a Gaussian distribution were presented as mean ± SD,*
*non-parametrically distributed variables as median [IQR],*
*† One-way ANOVA , ‡ chi-squared test , ¥ Kruskal-Wallis test*

**Table 6 :** Patient characteristics of the study population

In the analysis, there were included 134 patients, who were administered with biological agent for the first time (etanercept n=58, ustekinumab n=25, infliximab n=21, adalimumab n=30) for up to 8.9 years.

| Characteristics of Psoriasis | Etanercept N=58 | Ustekinumab N=25 | Infliximab N=21 | Adalimumab N=30 | p-value | All subjects N=134 |
|---|---|---|---|---|---|---|
| **Disease Characteristics** | | | | | | |
| Disease duration (yrs), median [IQR] | 16 [9.5-21.5] n=55 | 15 [12-23] n=23 | 17.5 [8.3-23] n=18 | 14 [7.3-20] n=28 | 0.780¥ | 15 [9-22] n=124 |
| Baseline PASI, median [IQR] | 14.8 [10.8-19.8] n=41 | 12 [10.5-21.6] n=17 | 14.4 [10.7-28] n=14 | 13.5 [10.5-18.2] n=24 | 0.676¥ | 14 [10.6-20.35] n=96 |
| Scalp lesions, % (no) | 74.1 (40/54) | 82.6 (19/23) | 55 (11/20) | 74.1 (20/27) | 0.254‡ | 72.6 (90/124) |
| Nails lesions, % (no) | 74.1 (40/54) | 69.6 (16/23) | 70 (14/20) | 63 (17/27) | 0.779‡ | 70.2 (87/124) |
| **Type of Psoriasis**, % (no) | | | | | | |
| plaque | 77.1 (37/48) | 73.9 (17/23) | 81 (17/21) | 92 (23/25) | 0.934‡ | 80.3 (94/117) |
| guttate | 8.3 (4/48) | 13 (3/23) | 14.3 (3/21) | 4 (1/25) | | 9.4 (11/117) |
| pustular | 4.2 (2/48) | 0 | 0 | 0 | | 1.7 (2/117) |
| inverse | 6.3 (3/48) | 8.7 (2/23) | 4.7 (1/21) | 4 (1/25) | | 6 (7/117) |
| erythrodermic | 4.2 (2/48) | 4.4 (1/23) | 0 | 0 | | 2.6 (3/117) |
| **Psoriatic Arthritis** | 47.2 (25/53) | 36.4 (8/22) | 55 (11/20) | 69.2 (18/26) | 0.125‡ | 51.2 (62/121) |
| **Comorbidities**, % (no) | | | | | | |
| Coronary Heart Disease | 25.5 (13/51) | 26.3 (5/19) | 10 (2/20) | 20.8 (5/24) | 0.541‡ | 21.9 (25/114) |
| Diabetes Mellitus II | 16.4 (9/55) | 26.1 (6/23) | 15 (3/20) | 13.3 (4/30) | 0.658‡ | 17.2 (22/128) |
| Hypertension | 40 (22/55) | 33.3 (7/21) | 23.8 (5/21) | 34.5 (10/29) | 0.662‡ | 34.9 (44/126) |
| Dyslipidemia | 40 (22/55) | 22.7 (5/22) | 30 (6/20) | 37.9 (11/29) | 0.520‡ | 34.9 (44/126) |

*numbers in brackets : numbers of individuals/number of individuals with data available,*
*Variables with a Gaussian distribution were presented as mean ± SD,*
*non-parametrically distributed variables as median [IQR],*
*† One-way ANOVA , ‡ chi-squared test , ¥ Kruskal-Wallis test*

**Table 7 :** Characteristics of psoriasis in the study population

| Treatment Characteristics | Etanercept N=58 | Ustekinumab N=25 | Infliximab N=21 | Adalimumab N=30 | p-value | All subjects N=134 |
|---|---|---|---|---|---|---|
| **Concomitant Treatment**, % (no) | | | | | | |
| none | 84.5 (49/58) | 76 (19/25) | 71.4 (15/21) | 85.7 (24/28) | | 81.1 (107/132) |
| Methotrexate | 8.6 (5/58) | 20 (5/25) | 19.1 (4/21) | 7.1 (2/28) | 0.441‡ | 12.1 (16/132) |
| Cyclosporine | 3.5 (2/58) | 0 | 9.5 (2/21) | 7.1 (2/28) | | 4.5 (6/132) |
| Retinoid | 3.5 (2/58) | 4 (1/25) | 0 | 0 | | 2.3 (3/132) |
| **Treatment Duration** (weeks), median [IQR] | 77.3 [31.6-154.8] n=50 | 152.1 [78.3-222.5] n=23 | 86.7 [26.1-187.1] n=21 | 52.1 [29.3-106.7] n=27 | **0.073**¥ | 82.3 [39-173.9] n=121 |
| **Number of previous systemic treatments**, % (no) | | | | | | |
| none | 20.4 (10/49) | 4.8 (1/21) | 16.7 (3/18) | 25 (6/24) | | 17.9 (20/112) |
| 1 | 59.2 (29/49) | 47.6 (10/21) | 44.4 (8/18) | 54.2 (13/24) | 0.313‡ | 53.6 (60/112) |
| 2 | 18.4 (9/49) | 42.9 (9/21) | 33.3 (6/18) | 20.8 (5/24) | | 25.9 (29/112) |
| 3 | 2 (1/49) | 4.8 (1/21) | 5.6 (1/18) | 0 | | 2.7 (3/112) |
| **Start during/after 2009**, % (no) | 54.6 (30/55) | 100 (24/24) | 61.9 (13/21) | 83.3 (25/30) | **<0.001**‡ | 70.8 ((92/130) |
| **Switch biological agent**, % (no) | 48.3 (28/58) | 16 (4/25) | 66.7 (14/21) | 50 (15/30) | **0.003**‡ | 45.5 (61/134) |
| **Status at the end of the study**, % (no) | | | | | | |
| **censored,** % (no) | 29.3 (17/58) | 64 (16/25) | 38.1 (8/21) | 50 (15/30) | | 41.8 (56/134) |
| continues | 13.8 (8/58) | 32 (8/25) | 14.3 (3/21) | 23.3 (7/30) | | (26/134) |
| lost to follow up | 15.5 (9/58) | 32 (8/25) | 23.8 (5/21) | 26.7 (8/30) | | (30/134) |
| **discontinuation,** % (no) | 70.7 (41/58) | 36 (9/25) | 61.9 (13/21) | 50 (15/30) | | 58.2 (78/134) |
| lack of effectiveness / loss of response | 36.2 (21/58) | 12 (3/25) | 33.3 (7/21) | 40 (12/30) | **0.015**‡ | 32.1 (43/134) |
| adverse event | 13.8 (8/58) | 4 (1/25) | 23.8 (5/21) | 6.7 (2/30) | | 11.9 (16/134) |
| patient's choice / insurance | 20.7 (12/58) | 20 (5/25) | 4.8 (1/21) | 3.3 (1/30) | | 14.2 (19/134) |

*numbers in brackets : numbers of individuals/number of individuals with data available,*
*Variables with a Gaussian distribution were presented as mean ± SD,*
*non-parametrically distributed variables as median [IQR],*
*† One-way ANOVA , ‡ chi-squared test , ¥ Kruskal-Wallis test*

**Table 8 :** Treatment characteristics in the study population

- Exploratory Analysis :

  We can combine the components of metabolic syndrome (hypertension, diabetes mellitus II, dyslipidemia, central obesity=BMI>30kg/$m^2$) in one bivariate variable "metabolic component", with positive value if having at least one of these comorbidities positive. As "comorbidity" we can examine the bivariate variable which is positive if a patient has positive metabolic component or coronary heart disease. Moreover, BMI has been distributed in 5 categories according to WHO.

| | Etanercept N=58 | Ustekinumab N=25 | Infliximab N=21 | Adalimumab N=28 | p-value | All subjects N=134 |
|---|---|---|---|---|---|---|
| **Metabolic component**, % (no) | 69.8 (37/53) | 60 (12/20) | 60 (12/20) | 79.3 (23/29) | 0.389‡ | 68.9 (84/122) |
| **Comorbidity** | 77/4 (41/53) | 70 (14/20) | 70 (14/20) | 86.2 (25/29) | 0.453‡ | 77 (94/122) |
| **BMI categorical** ($kg/m^2$), % (no) | | | | | | |
| [18.5,25) - normal | 9.6 (5/52) | 22.2 (4/18) | 31.6 (6/19) | 28.6 (8/28) | | 19.7 (23/117) |
| [25,30) - overweight | 51.9 (27/52) | 44.4 (8/18) | 15.8 (3/19) | 42.9 (12/28) | | 42.7 (50/117) |
| [30,35) - obese class I | 26.9 (14/52) | 22.2 (4/18) | 42.1 (8/19) | 17.9 (5/28) | **0.073**‡ | 26.5 (31/117) |
| [35,40) - obese class II | 7.7 (4/52) | 0 | 10.5 (2/19) | 3.6 (1/28) | | 6 (7/117) |
| [40,50) - obese class III | 3.9 (2/52) | 11.1 (2/18) | 0 | 7.1 (2/28) | | 5.1 (6/117) |

*numbers in brackets : numbers of individuals/number of individuals with data available,*
*‡ chi-squared test*

**Table 9 :** Exploratory analysis in the study population

The most common biological agent among bionaive patients was etanercept (n=58), followed by adalimumab (n=30), ustekinumab (n=25) and infliximab (n=21). More than a half of the subjects were male (59.7%), median age at the onset of therapy was 46 years, median baseline BMI was 28.5 $kg/m^2$. Demographic, disease and treatment characteristics were generally comparable across the 4 treatment groups. Plaque psoriasis was the dominant type of psoriasis (80.3%) and 31.9% of the patients reported a positive family history of psoriasis. The duration of psoriasis ranged from 9 to 22 years, with median value of 15 years. Baseline PASI score was generally similar across the different drug groups, with a median value of 14.

Patients treated with infliximab were more likely to use a concomitant treatment (28.6%) when compared to the other biological agents, with MTX use as the most common (12.1%) in the whole cohort. Nearly half of the group had already been treated with 1 systemic drug (53.6%) and 17.9% with none. 45.5% of all the patients decides to switch to another biological agent. 66.7% of patients discontinued infliximab compared with 50% of the adalimumab and 48.3% of the etanercept group. Only 16% of the ustekinumab group patients reached the decision to switch. Lack of effectiveness/loss of response was the most common reason for discontinuation of the treatment for the groups of etanercept, infliximab and adalimumab, whereas the majority of patients in the ustekinumab group stopped due to insurance or patient's choice. 70.8% of patients in the cohort initiated the treatment with biological agent during or after 2009, when all 4 drugs were on the greek (european) market.

The exploratory analysis indicated that the percentage of patients in the whole cohort with at least one component of the metabolic syndrome (hypertension, diabetes mellitus II, dyslipidemia, central obesity=BMI>30kg/m2) was 68.9%, according to their medical history. When comorbidity was defined as one component of the metabolic syndrome or coronary heart disease, the percentage reached the level of 77% of the psoriatic patients. Manifestation of more patients with infliximab having BMI in the category [30,35) is apparent (obese class I), when BMI is divided in the 5 categories as WHO recommends. The majority of the rest psoriatic patients belongs to the [25,30) category, meaning pre-obese status.

## 5.2 : Drug survival models with confounder correction

- **Overall drug survival**

The overall drug survival, independent of any biological agent was found at 110.9 weeks (2.13 years) in 76 events out of 121 subjects. (quantiles : 25$^{th}$=41.3 weeks, 50$^{th}$=110.9 weeks, 75$^{th}$=260.9 weeks). The relevant Kaplan-Meier curve follows.

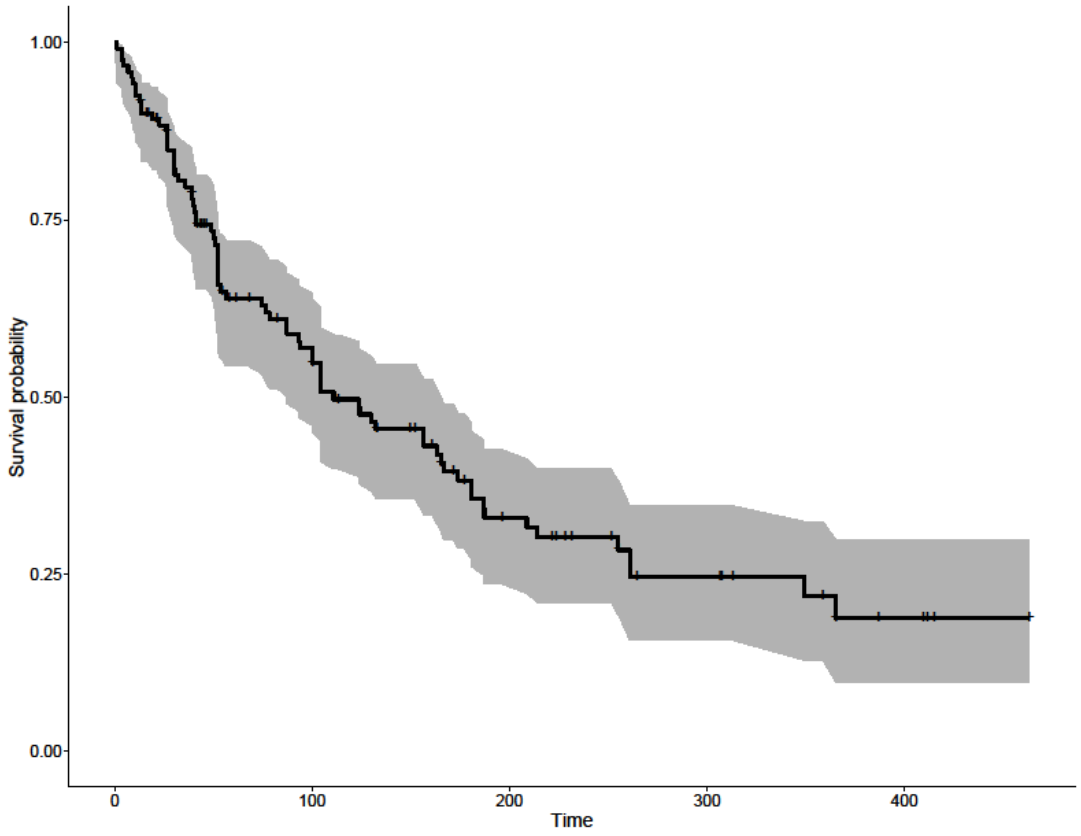



**Figure 3 :** Kaplan-Meier curve for the overall drug survival

- **Drug Survival Analysis per biological agent**

(n=121, 76 events, 14 observations deleted due to missingness)

| **Etanercept :** 37 events / 50 patients | | | | | | |
|---|---|---|---|---|---|---|
| Time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
| 1.00 | 50 | 1 | 0.980 | 0.0198 | 0.9420 | 1.000 |
| 8.71 | 49 | 1 | 0.960 | 0.0277 | 0.9072 | 1.000 |
| 8.86 | 48 | 1 | 0.940 | 0.0336 | 0.8764 | 1.000 |
| 10.43 | 47 | 1 | 0.920 | 0.0384 | 0.8478 | 0.998 |
| 13.00 | 46 | 0 | 0.920 | 0.0384 | 0.8478 | 0.998 |
| 13.14 | 45 | 1 | 0.900 | 0.0426 | 0.8198 | 0.987 |
| 16.00 | 44 | 0 | 0.900 | 0.0426 | 0.8198 | 0.987 |
| 26.29 | 43 | 2 | 0.858 | 0.0499 | 0.7654 | 0.961 |
| 29.86 | 41 | 3 | 0.795 | 0.0579 | 0.6892 | 0.917 |
| 30.29 | 38 | 1 | 0.774 | 0.0600 | 0.6649 | 0.901 |
| 35.71 | 37 | 1 | 0.753 | 0.0619 | 0.6410 | 0.885 |
| 39.29 | 36 | 1 | 0.732 | 0.0637 | 0.6175 | 0.868 |
| 41.71 | 35 | 0 | 0.732 | 0.0637 | 0.6175 | 0.868 |
| 43.29 | 34 | 0 | 0.732 | 0.0637 | 0.6175 | 0.868 |
| 44.00 | 33 | 0 | 0.732 | 0.0637 | 0.6175 | 0.868 |
| 52.14 | 32 | 2 | 0.686 | 0.0674 | 0.5663 | 0.832 |
| 52.29 | 30 | 2 | 0.641 | 0.0703 | 0.5168 | 0.794 |
| 56.29 | 28 | 1 | 0.618 | 0.0714 | 0.4926 | 0.775 |
| 61.43 | 27 | 0 | 0.618 | 0.0714 | 0.4926 | 0.775 |
| 76.29 | 26 | 1 | 0.594 | 0.0725 | 0.4677 | 0.754 |
| 78.29 | 25 | 1 | 0.570 | 0.0734 | 0.4432 | 0.734 |
| 87.14 | 24 | 1 | 0.547 | 0.0741 | 0.4190 | 0.713 |
| 92.86 | 23 | 1 | 0.523 | 0.0746 | 0.3953 | 0.691 |
| 100.00 | 22 | 1 | 0.499 | 0.0749 | 0.3719 | 0.670 |
| 100.14 | 21 | 1 | 0.475 | 0.0750 | 0.3488 | 0.647 |
| 104.29 | 20 | 1 | 0.451 | 0.0749 | 0.3262 | 0.625 |
| 104.43 | 19 | 1 | 0.428 | 0.0746 | 0.3038 | 0.602 |
| 110.86 | 18 | 1 | 0.404 | 0.0742 | 0.2819 | 0.579 |
| 124.00 | 17 | 1 | 0.380 | 0.0735 | 0.2603 | 0.555 |
| 130.00 | 16 | 1 | 0.356 | 0.0727 | 0.2390 | 0.531 |
| 132.29 | 15 | 1 | 0.333 | 0.0716 | 0.2182 | 0.507 |
| 149.57 | 14 | 0 | 0.333 | 0.0716 | 0.2182 | 0.507 |
| 156.57 | 13 | 1 | 0.307 | 0.0705 | 0.1958 | 0.482 |
| 160.71 | 12 | 0 | 0.307 | 0.0705 | 0.1958 | 0.482 |
| 166.57 | 11 | 1 | 0.279 | 0.0694 | 0.1715 | 0.454 |
| 187.00 | 10 | 1 | 0.251 | 0.0678 | 0.1480 | 0.427 |
| 196.29 | 9 | 0 | 0.251 | 0.0678 | 0.1480 | 0.427 |
| 214.00 | 8 | 1 | 0.220 | 0.0662 | 0.1218 | 0.397 |
| 254.71 | 7 | 1 | 0.188 | 0.0638 | 0.0971 | 0.366 |
| 255.14 | 6 | 0 | 0.188 | 0.0638 | 0.0971 | 0.366 |
| 260.86 | 5 | 1 | 0.151 | 0.0612 | 0.0681 | 0.334 |
| 349.29 | 4 | 1 | 0.113 | 0.0563 | 0.0426 | 0.300 |
| 409.57 | 3 | 0 | 0.113 | 0.0563 | 0.0426 | 0.300 |
| 411.57 | 2 | 0 | 0.113 | 0.0563 | 0.0426 | 0.300 |
| 463.14 | 1 | 0 | 0.113 | 0.0563 | 0.0426 | 0.300 |

**Table 10 :** Drug survival of etanercept

| **Ustekinumab :** 8 events / 23 patients | | | | | | |
|---|---|---|---|---|---|---|
| Time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
| 17.0 | 23 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 19.0 | 22 | 1 | 0.955 | 0.0444 | 0.871 | 1.000 |
| 46.3 | 21 | 0 | 0.955 | 0.0444 | 0.871 | 1.000 |
| 50.0 | 20 | 1 | 0.907 | 0.0628 | 0.792 | 1.000 |
| 53.4 | 19 | 1 | 0.859 | 0.0755 | 0.723 | 1.000 |
| 74.3 | 18 | 1 | 0.811 | 0.0851 | 0.661 | 0.996 |
| 82.3 | 17 | 0 | 0.811 | 0.0851 | 0.661 | 0.996 |
| 104.4 | 16 | 1 | 0.761 | 0.0936 | 0.598 | 0.968 |
| 123.9 | 15 | 1 | 0.710 | 0.1002 | 0.538 | 0.936 |
| 132.6 | 14 | 0 | 0.710 | 0.1002 | 0.538 | 0.936 |
| 132.9 | 13 | 0 | 0.710 | 0.1002 | 0.538 | 0.936 |
| 152.1 | 12 | 0 | 0.710 | 0.1002 | 0.538 | 0.936 |
| 165.3 | 11 | 0 | 0.710 | 0.1002 | 0.538 | 0.936 |
| 173.9 | 10 | 1 | 0.639 | 0.1125 | 0.452 | 0.902 |
| 177.0 | 9 | 0 | 0.639 | 0.1125 | 0.452 | 0.902 |
| 208.7 | 8 | 1 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 221.4 | 7 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 223.6 | 6 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 228.1 | 5 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 231.4 | 4 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 251.4 | 3 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 264.6 | 2 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |
| 313.1 | 1 | 0 | 0.559 | 0.1236 | 0.362 | 0.862 |

| **Infliximab :** 13 events / 21 patients | | | | | | |
|---|---|---|---|---|---|---|
| Time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
| 3.86 | 21 | 1 | 0.952 | 0.0465 | 0.8655 | 1.000 |
| 6.71 | 20 | 1 | 0.905 | 0.0641 | 0.7875 | 1.000 |
| 10.29 | 19 | 1 | 0.857 | 0.0764 | 0.7198 | 1.000 |
| 12.86 | 18 | 1 | 0.810 | 0.0857 | 0.6579 | 0.996 |
| 20.86 | 17 | 0 | 0.810 | 0.0857 | 0.6579 | 0.996 |
| 26.14 | 16 | 0 | 0.810 | 0.0857 | 0.6579 | 0.996 |
| 39.00 | 15 | 1 | 0.756 | 0.0955 | 0.5898 | 0.968 |
| 40.14 | 14 | 1 | 0.702 | 0.1028 | 0.5265 | 0.935 |
| 45.14 | 13 | 0 | 0.702 | 0.1028 | 0.5265 | 0.935 |
| 50.57 | 12 | 1 | 0.643 | 0.1096 | 0.4605 | 0.898 |
| 86.71 | 11 | 1 | 0.585 | 0.1142 | 0.3987 | 0.857 |
| 104.43 | 10 | 1 | 0.526 | 0.1168 | 0.3406 | 0.813 |
| 163.00 | 9 | 1 | 0.468 | 0.1175 | 0.2858 | 0.765 |
| 165.14 | 8 | 1 | 0.409 | 0.1165 | 0.2343 | 0.715 |
| 171.57 | 7 | 0 | 0.409 | 0.1165 | 0.2343 | 0.715 |
| 187.14 | 6 | 1 | 0.341 | 0.1153 | 0.1758 | 0.662 |
| 260.86 | 5 | 1 | 0.273 | 0.1106 | 0.1233 | 0.604 |
| 306.57 | 4 | 0 | 0.273 | 0.1106 | 0.1233 | 0.604 |
| 307.43 | 3 | 0 | 0.273 | 0.1106 | 0.1233 | 0.604 |
| 365.14 | 2 | 1 | 0.136 | 0.1112 | 0.0276 | 0.674 |
| 386.86 | 1 | 0 | 0.136 | 0.1112 | 0.0276 | 0.674 |

**Table 11 :** Drug survival of ustekinumab and infliximab

| **Adalimumab :** 15 events / 27 patients | | | | | | |
|---|---|---|---|---|---|---|
| Time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
| 3.57 | 27 | 1 | 0.963 | 0.0363 | 0.8943 | 1.000 |
| 4.43 | 26 | 1 | 0.926 | 0.0504 | 0.8322 | 1.000 |
| 13.14 | 25 | 1 | 0.889 | 0.0605 | 0.7779 | 1.000 |
| 21.43 | 24 | 0 | 0.889 | 0.0605 | 0.7779 | 1.000 |
| 22.29 | 23 | 1 | 0.850 | 0.0691 | 0.7250 | 0.997 |
| 26.14 | 22 | 1 | 0.812 | 0.0760 | 0.6755 | 0.975 |
| 26.71 | 21 | 1 | 0.773 | 0.0816 | 0.6284 | 0.951 |
| 31.86 | 20 | 1 | 0.734 | 0.0862 | 0.5834 | 0.924 |
| 39.00 | 19 | 0 | 0.734 | 0.0862 | 0.5834 | 0.924 |
| 39.86 | 18 | 1 | 0.694 | 0.0906 | 0.5369 | 0.896 |
| 41.14 | 17 | 1 | 0.653 | 0.0940 | 0.4922 | 0.866 |
| 41.29 | 16 | 1 | 0.612 | 0.0965 | 0.4491 | 0.834 |
| 49.00 | 15 | 1 | 0.571 | 0.0984 | 0.4075 | 0.800 |
| 52.14 | 14 | 2 | 0.490 | 0.0998 | 0.3283 | 0.730 |
| 54.43 | 12 | 0 | 0.490 | 0.0998 | 0.3283 | 0.730 |
| 57.86 | 11 | 0 | 0.490 | 0.0998 | 0.3283 | 0.730 |
| 68.00 | 10 | 0 | 0.490 | 0.0998 | 0.3283 | 0.730 |
| 93.57 | 9 | 1 | 0.435 | 0.1025 | 0.2743 | 0.690 |
| 100.29 | 8 | 0 | 0.435 | 0.1025 | 0.2743 | 0.690 |
| 113.14 | 7 | 0 | 0.435 | 0.1025 | 0.2743 | 0.690 |
| 156.57 | 6 | 1 | 0.363 | 0.1080 | 0.2022 | 0.650 |
| 180.29 | 5 | 1 | 0.290 | 0.1081 | 0.1398 | 0.602 |
| 180.71 | 4 | 1 | 0.218 | 0.1025 | 0.0864 | 0.548 |
| 358.71 | 3 | 0 | 0.218 | 0.1025 | 0.0864 | 0.548 |
| 365.29 | 2 | 0 | 0.218 | 0.1025 | 0.0864 | 0.548 |
| 415.14 | 1 | 0 | 0.218 | 0.1025 | 0.0864 | 0.548 |

**Table 12 :** Drug survival of adalimumab

According to the logrank test, the distributions of drug survival are different among the biological agents in a statistically significant degree (p-value=0.033), at the level of a=0.05.

| Biological Agent | **25$^{th}$ Quantile** | **50$^{th}$ Quantile** (median) | **75$^{th}$ Quantile** |
|---|---|---|---|
| **Etanercept** | 39.3 | 100 (1.92 yrs) | 214 |
| **Ustekinumab** | 123.86 | - | - |
| **Infliximab** | 40.14 | 163 (3.13 yrs) | 365.1 |
| **Adalimumab** | 31.86 | 52.1 (1yr) | 180.71 |

**Table 13** : Comparison of quantiles of drug survival (weeks) among the 4 treatment groups

The drug survival in the 50$^{th}$ and the 75$^{th}$ quantiles for ustekinumab could not be estimated from a Kaplan Meier curve, as less than 50% or 75% of the observations respectively are uncensored and the largest observation is censored (Figure 4). According to the drug survival analysis, ustekinumab has the longest drug survival. Among the anti-TNF-α factors, infliximab has the longest drug survival (median drug survival=3.13 years), followed by etanercept (median drug survival=1.92 years) and adalimumab (median drug survival=1 year).

Applying the restricted mean approach, by setting the upper limit to 401 weeks (the max treatment duration), we conclude that ustekinumab had the longest mean drug survival, at 274 weeks (5.27 years). Infliximab is second with 174 weeks (3.35 years) with adalimumab (146 weeks or 2.81 years) and etanercept (138 weeks or 2.65 years) following. The order of adalimumab and etanercept is reversed in mean drug survival as it was when median drug survival was measured (Table 14).

| | n | events | *rmean | *SE (rmean) | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|---|---|
| **Etanercept** | 50 | 37 | 138 | 19.3 | 100.0 | 56.3 | 157 |
| **Ustekinumab** | 23 | 8 | 274 | 34.9 | NA | 173.9 | NA |
| **Infliximab** | 21 | 14 | 174 | 34.5 | 163.0 | 50.6 | NA |
| **Adalimumab** | 27 | 17 | 146 | 32.5 | 52.1 | 41.1 | NA |
| * restricted mean with upper limit = 401 | | | | | | | |

**Table 14** : Comparison of drug survival (weeks) among the 4 treatment groups

When adjusting for gender and age at the onset of the treatment (as categorical bivariate variable with cut-off: >45 years), as well as the initiation of the drug during/after or before 2009, the difference among the distributions of drug survival is still significant (stratified log-rank test: p-value=0.048), at the level of a=0.05.

| **Treatment Duration** (weeks) | **Etanercept N=50** | **Ustekinumab N=23** | **Infliximab N=21** | **Adalimumab N=27** | **All subjects N=121** |
|---|---|---|---|---|---|
| **1year** (52) | 32 (64%) | 19 (82.6%) | 11 (52.4)% | 14 (51.9%) | 76 (62.8%) |
| **2 years** (104) | 20 (40%) | 16 (69.6%) | 10 (47.6%) | 7 (25.9%) | 53 (43.8%) |
| **3 years** (156) | 13 (26%) | 11 (47.8%) | 9 (42.9%) | 6 (22.2%) | 39 (32.2%) |
| **4 years** (208) | 8 (16%) | 8 (34.8%) | 5 (23.8%) | 3 (11.1%) | 24 (19.8%) |
| **5 years** (260) | 5 (10%) | 2 (8.7%) | 5 (23.8%) | 3 (11.1%) | 15 (12.4%) |
| **6 years** (312) | 4 (8%) | 1 (4.3%) | 2 (9.5%) | 3 (11.1%) | 10 (8.3%) |
| **7 years** (364) | 3 (6%) | 0 | 2 (9.5%) | 2 (7.4%) | 7 (5.8%) |
| **8 years** (416) | 1 (2%) | 0 | 0 | 0 | 1 (0.8%) |

**Table 15 :** Distribution of subjects who continue for at least 1 year their treatment during follow up

During three years of treatment, overall drug survival was the highest for ustekinumab, in accordance with previous studies (see Chapter 2). In more detail, at the treatment duration of 1 year: ustekinumab=82.6%, etanercept=64%, inflixmab=52.4% and adalimumab=51.9%, while at the treatment duration of 3 years: ustekinumab=47.8%, etanercept=26%, inflixmab=42.9% and adalimumab=22.2%, demonstrating the better performance of infliximab over etanercept and adalimumab as the time of treatment increases.

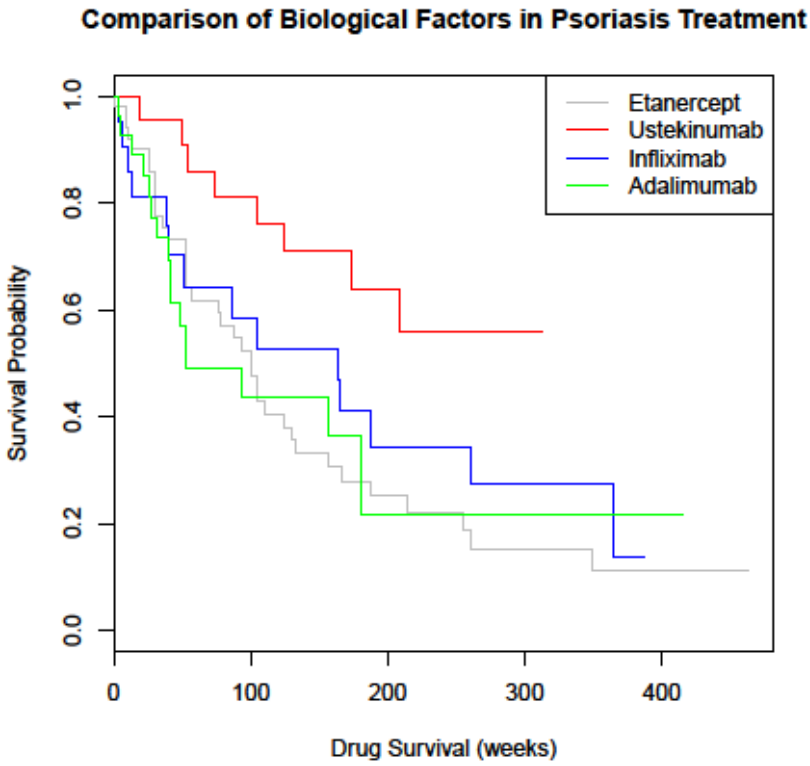



**Figure 4 :** Kaplan Meier curves for the drug survival of the 4 biological agents

It is apparent form the graphs presented above that the group of patients treated with ustekinumab as their first biological agent is less likely to discontinue the therapy, therefore ustekinumab has the longest drug survival.

## 5.3 : Cox Regression Analysis for Drug Survival

n=107, 70 events, 27 observations deleted due to missingness

| | Adjusted Hazard Ratio (HR) | 95% CIs | p-value | Wald test p-value |
|---|---|---|---|---|
| **Biological Agent** | | | | 0.052 |
| **etanercept** vs ustekinumab | **4.57** | (1.55,13.43) | 0.006 | |
| **infliximab** vs ustekinumab | 3.46 | (1.10,10.86) | 0.033 | |
| **adalimumab** vs ustekinumab | 3.85 | (1.29,11.49) | 0.016 | |
| **Gender** (female vs male) | 1.38 | (0.82,2.32) | 0.224 | |
| **Age at onset of treatment** (yrs) | 1.00 | (0.98,1.03) | 0.603 | |
| **Start during/after vs before 2009** | 1.37 | (0.77,2.45) | 0.285 | |
| **BMI categorical** ($kg/m^2$) | | | | 0.3902 |
| [25,30) vs [18.5,25) | 0.98 | (0.47,2.06) | 0.959 | |
| [30,35) vs [18.5,25) | 0.93 | (0.43,2.02) | 0.863 | |
| [35,40) vs [18.5,25) | 0.73 | (0.20,2.73) | 0.645 | |
| [40,50) vs [18.5,25) | 4.02 | (0.92,17.49) | 0.064 | |

**Table 16 :** Results of the Cox Regression model for drug survival

The hazard ratio of discontinuing the therapy of etanercept, infliximab and adalimumab in comparison to ustekinumab, adjusted for gender and age at the onset of the therapy as fixed variables, as well as the initiation of the drug during/after or before 2009, which was different among the 4 treatment groups at the statistical level of α=0.05 and the BMI at the statistical level of α=0.10.

As compared to ustekinumab, patients on etanercept (HR=4.57, 95%CI: 1.55,13.43), adalimumab (HR=3.85, 95%CIs: 1.29,11.49) or infliximab (HR=3.46, 95%CIs: 1.10,10.86) were more likely to discontinue therapy at statistically significant level (p-values=0.006, 0.016 and 0.033 respectively, <α=0.05), taking under account adjustment for gender, age at the onset of treatment, the initiation of treatment during/after 2009 and BMI. As a result, the longest drug survival was observed for ustekinumab, followed by anti-tumour necrosis agent (TNF)-a agents with the order being infliximab, adalimumab and etanercept (Table 16 and Figure 5).

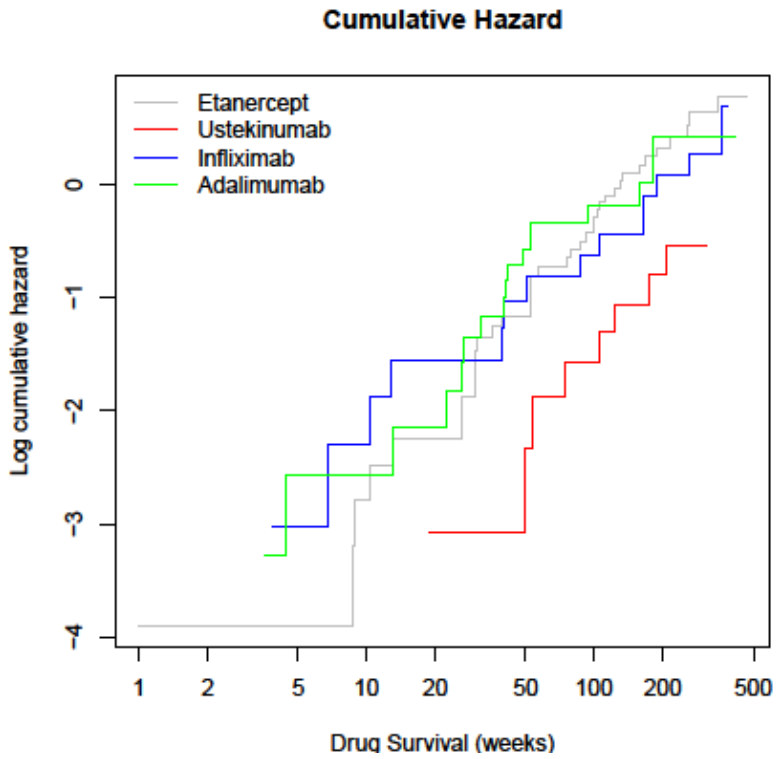



**Figure 5 :** Cumulative Hazard curves for the 4 biological agents

## 5.4 : Multivariate Cox Regression analysis for possible Predictors

- **Complete cases approach** :

n=73, events= 52

According to previous studies (see Chapter 2), the gender, age at onset of treatment, disease duration, baseline PASI, psoriatic arthritis, number of previous systemic treatments, BMI and concomitant treatment have been found to be predictors of discontinuation of the biological therapy in psoriasis. The year of initiation was examined as well.

In the initial evaluation of each variable with the inclusion criterion of p-value<0.2 for addition in the model of the biological agent, the variables of gender, number of previous systemic treatments, BMI (continuous, categorical) and concomitant treatment were selected. When multivariate analysis was performed for the identification of variables which are significant as possible predictors of discontinuation of the treatment (backward selection), the following variables were left in the final model: the biological agent, concomitant treatment with a systematic drug (MTX/ Cyclosporine/ Retinoid) and BMI as a categorical variable. This model was developed with the complete cases approach (no missing data).

| variable | p-value |
|---|---|
| Gender (female vs male) | 0.083 |
| Age at onset of treatment (yrs) | 0.605 |
| Disease duration (yrs) | 0.279 |
| Baseline PASI | 0.469 |
| Psoriatic Arthritis (yes vs no) | 0.765 |
| Number of previous systemic treatments (vs none) | 0.180 |
| BMI ($kg/m^2$) | 0.973 |
| BMI categorical ($kg/m^2$) (vs [18.5,25)) | 0.040 |
| Concomitant treatment (vs none) | 0.064 |
| Start during/after vs before 2009 | 0.825 |

*p-value presented in the table above refers to the LR-test between the bivariate model of each variable of this table and the biological agent and the univariate model of the biological agent*

**Table 17 :** Covariates examined in backwards selection method

| | Hazard Ratio (HR) | 95% CIs | p-value | Wald test p-value |
|---|---|---|---|---|
| **Biological Agent** | | | | 0.087 |
| **etanercept** vs Ustekinumab | 2.77 | (0.93,8.23) | 0.067 | |
| **infliximab** vs Ustekinumab | **4.66** | (1.31,16.50) | 0.017 | |
| **adalimumab** vs Ustekinumab | 3.75 | (1.19,11.80) | 0.024 | |
| **Concomitant treatment** | | | | 0.017 |
| MTX vs none | 0.40 | (0.16,1.02) | 0.055 | |
| Cyclosporine (CyA) vs none | 4.65 | (1.27,17.04) | 0.020 | |
| Retinoid vs none | 0.70 | (0.15,3.38) | 0.657 | |
| **BMI categorical** ($kg/m^2$) | | | | 0.008 |
| [25,30) vs [18.5,25) | 1.80 | (0.73,4.44) | 0.201 | |
| [30,35) vs [18.5,25) | 0.83 | (0.34,2.02) | 0.684 | |
| [35,40) vs [18.5,25) | 0.52 | (0.13,2.13) | 0.367 | |
| [40,50) vs [18.5,25) | 10.71 | (2.46,46.65) | 0.002 | |

**Table 18 :** Results of the multivariate Cox Regression model for drug survival (complete cases)

Results of this study were, in general, comparable to those from previous studies that included ustekinumab and TNF-a inhibitors. This issue will be further addressed in the Discussion topic (Chapter 6.1).

The multivariate analysis validated the finding of longest drug survival with ustekinumab in comparison to each TNF-a inhibitor. This time, the biological agent was a statistically significant variable overall in the model for the prediction of drug discontinuation in the statistical level of α=0.10 (Wald test p-value=0.087). Etanercept (HR=2.77, 95%CI: 0.93,8.23), adalimumab (HR=3.75, 95%CI: 1.19,11.80) and infiximab (HR=4.66, 95%CI: 1.31,16.50) are following.

The concomitant use of another systematic treatment acts as a significant predictor of discontinuation of the biological agent (Wald test p-value=0.017). It is worth mentioning that patients receiving MTX had significantly lower probability to discontinue the biological therapy (HR=0.4, 95, %CI: 0.16,1.02) compared to those without any concomitant treatment. Cyclosporine was found to be negative predictor of drug survival for patients on biological therapy (HR=4.65, 95, %CI: 1.27,17.04), however the low number of patients using CyA (6 patients) can influence the power of this

estimation. Use of retinoid drug was not proved to be significantly associated with drug discontinuation.

Consistent with recent studies (see Chapter 1), BMI was a significant positive predictor of discontinuation. Patients in the highest BMI category [40,50) kg/m$^2$) were more likely to discontinue their therapy (HR=10.71, 95%CI: 2.46,46.65), although the number of patients in this category is small (6 patients).

The assumption of proportional hazards in the model was assessed both graphically (Figure 6) and statistically by testing the Schoenfeld residuals: global chisq= 8.775, p-value=0.554.

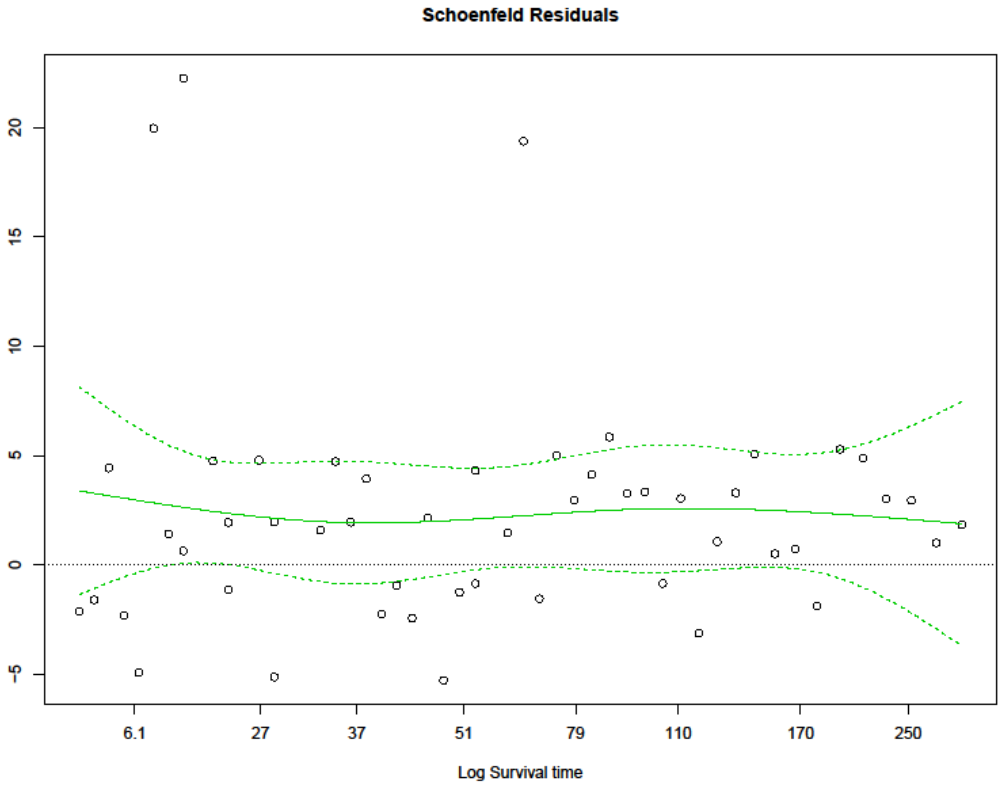



**Figure 6 :** Graphic assessment of the Schoenfeld residuals

- **Multiple imputation approach** :

The results of estimates from the 10$^{th}$ imputed dataset out of 10 imputed datasets are presented. Now, we can incorporate the baseline PASI is in the model. Imputation was not applied for the variable "duration of treatment", in order to maintain the nature of the main outcome (drug survival).

| | Hazard Ratio (HR) | 95% CIs | p-value | Wald test p-value |
|---|---|---|---|---|
| **Biological Agent** | | | | 0.031 |
| **etanercept** vs ustekinumab | 3.40 | (1.47,7.89) | 0.004 | |
| **infliximab** vs ustekinumab | **3.65** | (1.37,9.72) | 0.010 | |
| **adalimumab** vs ustekinumab | 3.06 | (1.25,7.49) | 0.014 | |
| **Concomitant treatment** | | | | 0.095 |
| MTX vs none | 0.81 | (0.39,1.68) | 0.574 | |
| Cyclosporine (CyA) vs none | 4.54 | (1.33,15.53) | 0.016 | |
| Retinoid vs none | 1.20 | (0.33,4.32) | 0.782 | |
| **BMI categorical** ($kg/m^2$) | | | | 0.212 |
| [25,30) vs [18.5,25) | 1.06 | (0.53,2.13) | 0.861 | |
| [30,35) vs [18.5,25) | 0.76 | (0.37,1.58) | 0.468 | |
| [35,40) vs [18.5,25) | 0.55 | (0.15,2.08) | 0.380 | |
| [40,50) vs [18.5,25) | 2.75 | (0.94,8.06) | 0.065 | |
| **baseline_PASI** | 0.99 | (0.97,1.01) | 0.346 | 0.346 |

**Table 19 :** Results of the multivariate Cox Regression model for drug survival (multiple imputation)

In this model, the biological agent remains significant. However, the differences between the hazard ratios among the 4 drugs are not so broad. We notice that in comparison with the reference ustekinumab, the group of patients treated with adalimumab (HR=3.06, 95%CI: 1.25,7.49), etanercept (HR=3.40, 95%CI: 1.47,7.89) and infliximab (HR=3.65, 95%CI: 1.37,9.72) are in greater risk of discontinuating their therapy. Etanercept and adalimumab are in reverse order to the complete cases model. This could be partially explained by the higher baseline PASI in the etanercept group (14.8) than in the adalimumab group (13.5).

As far as the rest of the covariates is concerned, an important notification is that the direction of the hazard ratios for concomitant use of MTX as a positive factor (HR=0.81, 95%CI: 0.39,1.68) to drug survival and CyA as a negative factor (HR=4.54, 95%CI: 1.33,15.53) in comparison with none is maintained.

Even though BMI is not a significant covariate in any level of statistical significance, the obese class III ([40,50) $kg/m^2$) group of psoriatic patients are still were more likely to discontinue their treatment (HR=2.75, 95%CI: 0.94,1.01).

The baseline PASI was not indicated as a possible predictor of the drug discontinuation.

## 5.5 : Subgroup analysis for psoriatic patients with psoriatic arthritis

The study population consisted of 51.2% (62/121) of patients with existing psoriatic arthritis at the moment of initializing the biological therapy. The distribution of this subgroup to the 4 biological agents was as following: enatercept (n=25), ustekinumab (n=8), infliximab (n=11) and adalimumab (n=18).

In general, patients had similar characteristics with the overall population of the study. One differential characteristic was the higher median age in the ustekinumab group (56 years old). The median treatment duration of psoriatic patients with psoriatic arthritis was shorter than in the whole

sample (64.7 weeks vs 82.3 weeks). In addition, a larger percentage of the patients discontinue therapy (66.7% vs 58.2%). 59.7% of the psoriatic arthritis subgroup decides to switch biological agent. In order to assess the effect of psoriatic arthritis to the likelihood of discontinuation of the biological therapy, we introduced the interaction term biological agent*psoriatic arthritis to the multivariate Cox Regression model presented in Chapter 5.4.

When the 2 models with and without the interaction term were compared with the lr-test, the result was a statistically significant effect in the level of $\alpha$=0.10 (p-value= 0.063).

| | **Hazard Ratio (HR)** | **95% CIs** | **p-value** | **Wald test p-value** |
|---|---|---|---|---|
| **Biological Agent** | | | | 0.151 |
| **etanercept** vs ustekinumab | 5.89 | (1.30,26.75) | 0.022 | |
| **infliximab** vs ustekinumab | 5.94 | (0.97,36.35) | 0.054 | |
| **adalimumab** vs ustekinumab | 18.50 | (3.30,103.69) | <0.001 | |
| **Concomitant treatment** | | | | 0.006 |
| MTX vs none | 0.35 | (0.14,0.91) | 0.032 | |
| Cyclosporine (CyA) vs none | 5.99 | (1.56,22.97) | 0.009 | |
| Retinoid vs none | 0.83 | (0.17,4.24) | 0.830 | |
| **BMI categorical** ($kg/m^2$) | | | | 0.002 |
| [25,30) vs [18.5,25) | 1.80 | (0.72,4.24) | 0.205 | |
| [30,35) vs [18.5,25) | 0.72 | (0.29,1.83) | 0.495 | |
| [35,40) vs [18.5,25) | 0.59 | (0.13,2.73) | 0.502 | |
| [40,50) vs [18.5,25) | 17.68 | (3.54,88.23) | <0.001 | |
| **Psoriatic Arthritis** (yes vs no) | 7.06 | (0.94,53.12) | 0.052 | 0.715 |
| **Interaction term : Biological Agent * Psoriatic Arthritis** (yes vs no) | | | | 0.046 |
| **etanercept** * **Psoriatic Arthritis** yes | 0.11 | (0.01,1.02) | 0.052 | |
| **infliximab** * **Psoriatic Arthritis** yes | 0.30 | (0.03,3.35) | 0.325 | |
| **adalimumab** * **Psoriatic Arthritis** yes | 0.04 | (0.004,0.47) | 0.010 | |

**Table 20 :** Results of the multivariate Cox Regression model for the effect of psoriatic arthritis on drug survival

The lowest hazard of treatment discontinuation was observed for ustekinumab, followed by anti-tumour necrosis agent (TNF)-a agents with the order being etanercept, infliximab and adalimumab (Table 20), whereas in the overall population sample the anti-TNF-a order was, etanercept, adalimumab and infliximab.

The overall median drug survival for psoriatic patients with psoriatic arthritis is 110.9 weeks, identical with the whole psoriatic population.

## 5.6 : Analysis of the drug efficacy

From the available data about the PASI score in the first year (the window described in Chapter 4.4.2):

| **PASI50 at year 1** | **Etanercept N=7** | **Ustekinumab N=8** | **Infliximab N=4** | **Adalimumab N=6** | **Total N=25** |
|---|---|---|---|---|---|
| continues after year 1 | 2/7 | 5/7 | 0/2 | 2/3 | 9/19 |
| lost to follow-up after year 1 | 0/0 | 0/0 | 0/0 | 1/1 | 1/1 |
| **Discontinuation at year 1 :** | 0/0 | 0/1 | 2/2 | 0/2 | 2/5 |
| lack of effectiveness / loss of response | 0/0 | 0/1 | 1/1 | 0/2 | 1/4 |
| adverse event | 0/0 | 0/0 | 1/1 | 0/0 | 1/1 |
| **Total :** at least 1 year | 2/7 (28.6%) | 5/8 (62.5%) | 2/4 (50%) | 3/6 (50%) | 12/25 (48%) |

**Table 21** : Drug efficacy measured as PASI50 at year 1, according to the status at the end of the study

Therefore, 12/25 patients (48%) in total achieve PASI50 in the first year, with the majority being treated with ustekinumab (62.5%).

| **PASI75 at year 1** | **Etanercept N=7** | **Ustekinumab N=8** | **Infliximab N=4** | **Adalimumab N=6** | **Total N=25** |
|---|---|---|---|---|---|
| continues after year 1 | 2/7 | 3/7 | 0/2 | 2/3 | 7/19 |
| lost to follow-up after year 1 | 0/0 | 0/0 | 0/0 | 0/1 | 0/1 |
| **Discontinuation at year 1 :** | 0/0 | 0/1 | 2/2 | 0/2 | 2/5 |
| lack of effectiveness / loss of response | 0/0 | 0/1 | 1/1 | 0/2 | 1/4 |
| adverse event | 0/0 | 0/0 | 1/1 | 0/0 | 1/1 |
| **Total :** at least 1 year | 2/7 (28.6%) | 3/8 (37.5%) | 2/4 (50%) | 2/6 (33.3%) | 9/25 (36%) |

**Table 22** : Drug efficacy measured as PASI75 at year 1, according to the status at the end of the study

Therefore, 9/25 patients (36%) in total achieve PASI75 in the first year, with the majority being treated with infliximab (2/4, 50%).

| **PASI90 at year 1** | **Etanercept N=7** | **Ustekinumab N=8** | **Infliximab N=4** | **Adalimumab N=6** | **Total N=25** |
|---|---|---|---|---|---|
| continues after year 1 | 2/7 | 2/7 | 0/2 | 1/3 | 5/19 |
| lost to follow-up after year 1 | 0/0 | 0/0 | 0/0 | 0/1 | 0/1 |
| **Discontinuation at year 1 :** | 0/0 | 0/1 | 2/2 | 0/2 | 2/5 |
| lack of effectiveness / loss of response | 0/0 | 0/1 | 1/1 | 0/2 | 1/4 |
| adverse event | 0/0 | 0/0 | 1/1 | 0/0 | 1/1 |
| **Total :** at least 1 year | 2/7 (28.6%) | 2/8 (25%) | 2/4 (50%) | 1/6 (16.7%) | 7/25 (28%) |

**Table 23** : Drug efficacy measured as PASI90 at year 1, according to the status at the end of the study

Therefore, 7/25 patients (28%) in total achieve PASI90 in the first year, with the majority being treated with infliximab (2/4, 50%).

| 1st year | Etanercept N=7 | Ustekinumab N=8 | Infliximab N=4 | Adalimumab N=6 | Total N=25 |
|---|---|---|---|---|---|
| **PASI50** | 2/7 (28.6%) | 5/8 (**62.5%**) | 2/4 (50%) | 3/6 (50%) | 12/25 (48%) |
| **PASI75** | 2/7 (28.6%) | 3/8 (37.5%) | 2/4 (**50%**) | 2/6 (33.3%) | 9/25 (36%) |
| **PASI90** | 2/7 (28.6%) | 2/8 (25%) | 2/4 (**50%**) | 1/6 (16.7%) | 7/25 (28%) |

**Table 24** : Drug efficacy measured as PASI50, PASI75 and PASI90 at year 1, in total.

When we consider the median change in PASI score from the baseline score to the score at year1 (window), we get the following table :

| | Etanercept N=7 | Ustekinumab N=8 | Infliximab N=4 | Adalimumab N=6 | Kruskal-Wallis test | Total N=25 |
|---|---|---|---|---|---|---|
| Baseline PASI, median [IQR] | 14.6 [8.4-17.5] | 13.1 [11.2-22] | 24.7 [12.8-35.3] | 21.1 [18.2-24.7] | 0.340¥ | 15 [11.4-23.3] |
| PASI at year 1, median [IQR] | 6.3 [2.7-9.8] | 5.7 [2.7-8.5] | 4.4 [0-12.7] | 9.9 [3.7-18.8] | 0.785¥ | 6.3 [1.5-12] |

**Table 25** : Absolute value of PASI score at year 1 in comparison to baseline.

A useful observation about this subgroup of patients with data at year 1 is that the subjects treated with infliximab and adalimumab have a higher baseline PASI than the overall population. Therefore, the results about these 2 biological subjects must be carefully interpreted, taking under consideration that it is not a representative sample of the study population.

# Chapter 6: Discussion

## 6.1 : Interpretation of Results - Comparison with previous studies

Our results were generally comparable to those from other studies that included ustekinumab and TNF-a inhibitors. The finding that in our study ustekinumab presents the best performance in both the 1-year and 3-year drug survival is in line with similar studies (see Chapter 2). Moreover, infliximab is the best among anti-TNF-α biological agents in long term drug survival (3-year), while in 1-year survival etanercept performs better. In the analysis of data from the Danish DERMIO registry, 40% of treatment episodes remained on adalimumab and etanercept and 70% of treatment episodes on infliximab for 4 years. It has been reported that, as a general rule, biologic therapies lose effectiveness over time[34].

In the interpretation of the covariates associated with discontinuation of the biological agent, we need to clarify that our method of forcing the drug to the multivariate model is possible to restrict the calling of the significant variables as possible predictive factors. Nevertheless, we found that gender was not a significant variable, in comparison with other studies which suggested the female gender as positive predictor of treatment withdrawal[60,62,63,65]. Other studies also demonstrated the statistically significant association of longer drug survival with higher age[62] and longer disease duration[62,65]. In the present study such associations could not be validated. Consistent with recent studies[66,103], BMI was a significant positive predictor of discontinuation in our study.

One important deviation from the current studies is the concomitant use of MTX as reducing the probabilities of the discontinuation of the biological agent. This result is in contradiction with other studies[60,65] that suggested MTX treatment was favorably associated with discontinuation of the biologic agent. One explanation could be the better effectiveness of the combined therapy, as MTX inhibits the formation of antibodies to the biological agent[49]. The development of antidrug antibodies to monoclonal antibodies such as infliximab and adalimumab promotes the reduction of the serum levels of the drug and the probability of retaining response to these drugs. On the contrary, patients are rare to develop antidrug antibodies to etanercept[104,105,106].

## 6.2 : Strengths of the study

One major advantage of the present study is the fact that data have been derived and extracted from daily clinical praxis and covers a long-term period of up to 8.9 years. This condition can provide medical research with datasets independent of the strict inclusion criteria of clinical trials. Moreover, we assess the first-time treatment of psoriatic patients with biological agent, avoiding the issues of anti-drug antibodies addressed in Chapter 1. Up to the time that this dissertation is completed, no similar study referring to the Greek population has been published, making our study quite original in that way. All in all, our results are in line with the current scientific literature.

## 6.3 : Limitations of the study

It is essential for the integrity of our results to acknowledge several limitations of the present study. As an observational study, it lacks of the randomization of patients to the 4 different drug groups. However, the most important limitation is the restricted availability of medical files and electronic records. Consequently, detailed information on the dosage of the drugs is absent and measurements of PASI scores suffer from many missing values. This is connected with the recall bias during the phone interviews with the patients for completion of their medical history, which could be a source of systematic error.

As a result, we recommend the development of a registry for psoriatic patients in Greece, like in many other countries. It could reinforce the correct input of all the necessary data for the conduction of future studies and support the possibility of multi-central studies, achieving larger samples and greater validity of the produced results.

# Chapter 7: Conclusion

Despite the acknowledged limitations of the present study, the main results remain robust and clear enough to suggest that ustekinumab has the longest drug survival among the 4 examined biological agents. Concomitant treatment with methotrexate and BMI seem to play a significant role in the discontinuation of the treatment.

Future studies need to be conducted in order to determine the optimal drug dosing, treatment schedule, and concomitant medications required. Moreover, the development of biostatistical methods that correlate treatment response with serum drug levels and potential biomarkers from pharmacogenetic studies, gene and miRNA expression profiling and epigenetic, flow cytometric, proteomic, and metabolomic studies would benefit the research on psoriasis[107-112].

Further investigation is necessary for the discovery and validation of biomarkers, such as the C-reactive protein, regarding the possible contribution of inflammatory control by biological therapy to the clinical improvement of the psoriatic patients in terms of cardiovascular and metabolic comorbidities[113]. Long-term studies are important in order to allow for the detection of rare adverse events in biological treatment.

At the moment, oral, small molecule technologies, such as apremilast and tofacitinib, and the three interleukin (IL)-17 inhibitors brodalumab, ixekizumab, and secukinumab are emerging in the research field of biological treatment of psoriasis. Furthermore, knowledge of the clinical pharmacology of anti-drug antibody production and determinants of non-adherence to therapy will enable minimum dosing and cost-effective prescribing. Also, biosimilar agents are gradually introduced into the psoriasis market as the current established TNF inhibitors lose patent protection[114].

In summary, biological agents have become the gold standard for the treatment of moderate-to-severe psoriasis in terms of efficacy, safety and quality of life for patients who have failed or have contraindications for traditional systemic treatments[115].

# Chapter 8: Summaries

## 8.1 : Summary in Greek - Περίληψη

**Τίτλος:** Επιβίωση Φαρμάκου σε ψωριασικούς ασθενείς που λαμβάνουν βιολογικό παράγοντα για πρώτη φορά

**Υπόβαθρο:** Μακροχρόνια δεδομένα καθημερινής κλινικής πράξης αποκλειστικά σε ψωριασικούς ασθενείς που δεν έχουν λάβει στο παρελθόν βιολογικό παράγοντα έχουν χρησιμοποιηθεί σπάνια για την ταυτοποίηση προγνωστικών παραγόντων της επιβίωσης φαρμάκου.
**Στόχοι**: Ο κύριος σκοπός ήταν η σύγκριση της μακροχρόνιας επιβίωσης ανάμεσα στο ustekinumab(UST) (IL-12/23 ανταγωνιστής) και τα etanercept(ETN), infliximab(INF) και adalimumab(ADL) (αντι-TNF παράγοντες). Δευτερεύον στόχος ήταν η αξιολόγηση προγνωστικών παραγόντων της επιβίωσης φαρμάκου και η ανάλυση σε υπο-ομάδες για την ψωριασική αρθρίτιδα.
**Μέθοδοι**: Δεδομένα από 12 έτη εξήχθησαν αναδρομικά από μία μονοκεντρική προοπτική κοορτή ψωριασικών ασθενών που δεν έχουν λάβει στο παρελθόν βιολογικό παράγοντα στην καθημερινή κλινική πράξη. Χρησιμοποιήθηκαν καμπύλες επιβίωσης Kaplan-Meier, log-rank έλεγχοι και πολυπαραγοντική Cox παλινδρόμηση με διόρθωση συγχυτικών παραγόντων. Η μέθοδος backward selection αξιοποιήθηκε για την ταυτοποίηση προγνωστικών παραγόντων της επιβίωσης φαρμάκου. Για την ανάλυση σε υπο-ομάδες χρησιμοποιήθηκε όρος αλληλεπίδρασης και για την επιβεβαίωση των αποτελεσμάτων της παλινδρόμησης εφαρμόστηκε η μέθοδος multiple imputations(MICE).
**Αποτελέσματα**: 134 ασθενείς συμπεριλήφηκαν; ETN=58, INF=21, ADL=30, UST=25. Έναρξη της θεραπείας κατά/μετά το 2009 έκανε το 70.8% της κοορτής, όταν όλοι οι βιολογικοί παράγοντες υπήρχαν στην αγορά. Τα ποσοστά επιβίωσης φαρμάκου είναι υψηλότερα για το UST μετά από 1 (UST=82.6%,ETN=64%,INF=52.4%,ADL=51.9%) και 3 έτη (UST=47.8%,ETN=26%,INF=42.9%,ADL=22.2%). Το INF παρουσιάζει καλύτερα αποτελέσματα από τα ETN και ADL καθώς αυξάνεται η διάρκεια της αγωγής. Το UST έχει την πιο μακρά διάμεση επιβίωση φαρμάκου ($25^{th}$ τεταρτημόριο=2.38 έτη). Ανάμεσα στους αντι-TNF παράγοντες, το INF έχει την πιο μακρά διάμεση επιβίωση φαρμάκου (3.13 έτη), ακολουθούμενο από το ETN (1.92 έτη) και το ADL (1 έτος). Σε σύγκριση με το UST, οι ασθενείς σε ETN (HR=4.57 95%CI:1.55,13.43), ADL (HR=3.85 95%CIs:1.29,11.49) ή INF (HR=3.46 95%CIs:1.10,10.86) βρίσκονταν σε σημαντικά μεγαλύτερο κίνδυνο να σταματήσουν τη θεραπεία, ελέγχοντας για το φύλο, ηλικία, έναρξη της αγωγής κατά/μετά το 2009 και το BMI. Η συνύπαρξη της ψωριασικής αρθρίτιδας δεν προκάλεσε κάποια σημαντική επίδραση υπο-ομάδων (lr-test:p-value=0.063). σημαντικός προγνωστικός παράγοντας της επιβίωσης φαρμάκου ήταν η ταυτόχρονη χρήση methotrexate (HR=0.4 95%CI: 0.16,1.02). Η cyclosporine ήταν αρνητικός προγνωστικός παράγοντας της επιβίωσης φαρμάκου (HR=4.65 95%CI: 1.27,17.04). Οι ασθενείς στην υψηλότερη κατηγορία BMI [40,50)$kg/m^2$ ήταν σε μεγαλύτερο κίνδυνο να σταματήσουν τη θεραπεία (HR=10.71 95%CI: 2.46,46.65).
**Συμπεράσματα**: Η πιο μακρά επιβίωση φαρμάκου, διορθωμένη για συγχυτικούς παράγοντες, παρατηρήθηκε για το UST, με τα INF, ADL και ETN να ακολουθούν. Η methotrexate είναι ένας θετικός παράγοντας για πιο μακρά επιβίωση φαρμάκου, ενώ η cyclosporine και το υψηλό BMI είναι αρνητικοί.

## 8.2 : Summary in English

**Title**: Drug Survival in psoriatic patients treated with biologic agent for the first time

**Background:** Long-term data restricted to biologic-naive psoriatic patients in daily praxis have rarely been used for the identification of predictors for drug survival.
**Objectives**: The main objective was to compare long-term drug survival among ustekinumab(UST) (IL-12/23 antagonist) and etanercept(ETN), infliximab(INF) and adalimumab(ADL) (anti-TNF agents). Secondary aim was the assessment of predictors for the drug survival and the subgroup analysis for psoriatic arthritis.
**Methods**: Data from 12 years were extracted retrospectively from a single-centre prospective cohort of biologic-naive psoriatic patients in daily praxis. Kaplan-Meier survival curves, log-rank tests and multivariate Cox regression analysis with confounder correction were performed. Backward selection was used for the identification of predictors for drug survival. Interaction was used for the subgroup analysis and multiple imputations(MICE) for the verification of the regression results.
**Results**: 134 patients were included; ETN=58, INF=21, ADL=30, UST=25. Initiation of therapy during/after 2009 made the 70.8% of the cohort, when all biologicals were in market. The drug survival rates are higher for UST after 1 (UST=82.6%,ETN=64%,INF=52.4%,ADL=51.9%) and 3 years (UST=47.8%,ETN=26%, INF=42.9%,ADL=22.2%). INF performs better than ETN and ADL as the time of treatment increases. UST has the longest median drug survival ($25^{th}$quantile=2.38 yrs). Among the anti-TNF factors, INF has the longest median drug survival (3.13 yrs), followed by ETN (1.92 yrs) and ADL (1year). As compared to UST, patients on ETN (HR=4.57 95%CI:1.55,13.43), ADL (HR=3.85 95%CIs:1.29,11.49) or INF (HR=3.46 95%CIs:1.10,10.86) were in significantly greater risk to discontinue therapy, while adjusting for gender, age, initiation of treatment during/after 2009 and BMI. Presence of psoriatic arthritis did not cause a significant subgroup effect (lr-test:p-value=0.063). Significant positive predictor of drug survival was the concomitant use of methotrexate (HR=0.4 95%CI: 0.16,1.02). Cyclosporine was a negative predictor of drug survival (HR=4.65 95%CI: 1.27,17.04). Patients in the highest BMI category [40,50)$kg/m^2$ were in greater risk to discontinue therapy (HR=10.71 95%CI: 2.46,46.65).
**Conclusions**: The longest drug survival corrected for confounders was observed for UST, followed by INF, ADL and ETN. Methotrexate is a positive determinant of longer biological drug survival, whereas cyclosporine and higher BMI are negative.

# Chapter 8: References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# Chapter 10: Appendix

## Abbreviations

ADA : anti-drug antibodies
ADL : adalimumab
CyA : cyclosporine
ETN : etanercept
INF : infliximab
MTX : methotrexate
TNF : tumor necrosis factor
UST : ustekinumab