Pharmacoeconomic aspect of moderate and severe psoriasis treatment with biological therapy versus conventional therapy

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This dissertation was made at the Department of Dermatology and Venereology, Sestre Milosrdnice University Hospital Center, and the University of Zagreb School of Medicine.

Mentors: Academician Mirna Šitum and Professor Stjepan Orešković

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CONTENT

ABBREVIATIONS

ALT - alanine transaminase

AST - aspartate transaminase

BP - blood pressure

BSA - body surface area

CBA - cost-benefit analysis

CBC - complete blood count

CEA - cost-effectiveness analysis

CKD - chronic kidney disease

CUA - cost-utility analysis

CV – cardiovascular

DBC - differential blood count

DLQI - Dermatology Life Quality Index

DMARD - disease-modifying antirheumatic drugs

DCER - decremental cost-effectiveness ratio

EP - erythrodermic psoriasis

ESRD - end-stage renal disease

FDA - Food and Drug Administration

GDP - gross domestic product

GGT – gamma-glutamyl transferase

HBV - hepatitis B virus

HCV - hepatitis C virus

HIV - human immunodeficiency virus

HLA - human leukocyte antigen

HRQoL - health-related quality of life

IBD - irritable bowel disease

ICER - incremental cost-effectiveness ratio

IGA - investigator's global assessment

IL - interleukin

IP - inverse psoriasis

MI - myocardial infarction

NAFLD - non-alcoholic fatty liver illness

NF - nuclear factor

NMB - net monetary benefit

PASI - psoriasis area and severity index

PGA - physician global assessment

PsA - psoriatic arthritis

PUVA - psoralen plus ultraviolet-A radiation

QALY - quality-adjusted life years

QoL - quality of life

RCT - randomized controlled trials

SC - subcutaneous

TB - tuberculosis

TNF - tumor necrosis factor

UV - ultraviolet

WTP - willingness to pay

1. INTRODUCTION

1.1. Definition

A chronic, long-lasting condition known as psoriasis is marked by the immune system's triggering, resulting in an accelerated proliferation of skin cells (1). It is a resistant, hereditary illness affecting skin, joints, or both (2). Erythematosquamous lesions most frequently develop on the scalp, elbows, or knees (1,2), but almost all body regions can also be affected. Although researchers are unaware of psoriasis's exact aetiology, they identify that it combines genetic and environmental factors (1).

Psoriasis is a widespread disease that substantially influences individuals and the healthcare sector (3). It is a complex chronic illness with a remitting/relapsing phase (4). This illness affects around 0.1-1.5% of the world's population. (5). The annual prevalence rate ranges from 50 to 140 novel occurrences per 100,000 individuals. The disease manifests and progresses in various ways, from minimally noticeable to widespread skin involvement and from stable to unstable presentations that alternate frequently (4).

1.2. Classifications of Psoriasis

Psoriasis is classified into two categories: cutaneous psoriasis and psoriasis with comorbidities. Cutaneous psoriasis is categorized as guttate, plaque, inverse, erythrodermic, and pustular psoriasis. Comorbidities such as arthritis, diabetes, pulmonary disease, central nervous system diseases, uveitis, cardiovascular disease, bowel disease, nephropathy, metabolic syndrome, and liver disease occur in systemic psoriasis (6).

1.2.1. Cutaneous Psoriasis

It is classified into the following types (6):

Plaque psoriasis is characterized by well-demarcated, erythematosquamous plaques (7). The severity of plaque psoriasis is estimated by erythema assessment, skin infiltration, or desquamation, and the percentage of the affected skin (6). Lesions in this type are most frequently located on the scalp, back, elbows and knees and may be itchy and painful when active. The patches are coloured differently depending on the skin tone of the patient. Lesions in patients with darker or black skin may leave transitory colour changes (8).

Scalp involvement in psoriasis ranges from moderate with only a few erythematosquamous plaques to the involvement of the entire scalp, which can extend beyond the border of the scalp and give a wrapped hair impression (6). Nails can also be affected in plaque psoriasis. One of the symptoms is nail pitting. Further manifestations on the nails include an oil-drop sign, nail bed splinter haemorrhages, and nail plate cracking or loosening. Notably, it is a strong predictor of psoriatic arthritis. At the time of diagnosis, nails are affected in around half of all cases, which adds to the social load and lowers the life quality in those individuals (6).

Guttate psoriasis is the type of disease that most commonly affects young individuals and kids (6,8). Typically, a Streptococcal infection triggers the disease. Small round drop-like lesions, are most commonly located on the chest and limbs (8). In adulthood, one-third of patients with guttate psoriasis will develop chronic plaque psoriasis (6).

Inverse psoriasis (IP) is also known as flexural or intertriginous psoriasis because it is located mainly in the body folds (6,9). The most commonly affected regions in this type are the inguinal and axillar folds, followed by the perineal region, the umbilicus, and the retroauricular zone. Lesions are typically erythematous but smooth, moist, and shiny, seldom covered by whitish scales. Due to sweating, lesions are often macerated. Irritation may lead to itching, which results in superficial erosion that may cause secondary infections. In infants, lesions are mainly found in the diaper region and inguinal folds, and the disease is popularly called napkin psoriasis (8,10). Patients with IP can also have lesions on other body areas (6).

Erythrodermic psoriasis (EP) is the very rare but the most severe form that affects almost the entire skin (8). Extensive skin involvement results in loss of homeostatic function of the skin and often have symptoms like fever, coldness, dehydration, lymph node swelling, GI discomfort, and loss of skeletal muscle and fat. These patients often need hospital monitoring (11). This form of psoriasis can, in extreme forms, be fatal (6).

Pustular psoriasis is a type of psoriasis with characteristic sterile pustules. They can develop in generalised pustular psoriasis when affecting more extensive body surfaces and localised pustular psoriasis with lesions on the palms or soles (8).

1.2.2. The Severity of Cutaneous Psoriasis

The severity classifications of cutaneous psoriasis are helpful for physicians for making treatment decisions and determining eligibility requirements for clinical investigations. The Body Surface Area - BSA, Psoriasis Area and Severity Index - PASI and Investigator's Global Assessment - IGA categorize skin psoriasis into three categories: mild, moderate and severe, which are presented in Table 1 (6,12).

Table 1: Categories based on severity (adopted from Feldman (12))

Tool Score	**Mild**	**Moderate**	**Severe**
BSA	< 3%	3% ≤ to < 10%	≥ 10%
PASI	< 3	3 ≤ to < 10	≥ 10
IGA	= 1	= 2	= 3/4

Body Surface Area (BSA) measures the area of skin affected by psoriasis based on the clinical examination and visual approximate calculation. (13).

Psoriasis area and severity index (PASI) is additionally used to assess the extent of psoriasis (6). It is an assessment tool that measures and scores the degree of severity of psoriatic symptoms as well as the reaction of the patient to therapy. It comes up with a number value between zero and seventy-two (0-72). A value between 5 and 10 is deliberated as moderate illness, while 10 or above is measured as severe illness (14).

Investigator's global assessment (IGA) is not commonly used in Croatia, but in other countries, IGA is part of physicians' evaluation. In psoriasis, investigator global evaluations, also known as physician global assessments (PGA), consist of a subjective estimate of psoriasis severity. There are several variants of IGA, each with its own set of instructions, type of scale and counting system (15).

The scale can be either dynamic or static. Static global evaluation measures are based on one evaluation of the severity of the disease at a particular moment in a time. The static IGA (Table 2) metric may designate a patient's psoriasis illness's aggressiveness as "moderate" at any particular moment. On the other hand, dynamic global evaluation compares current illness severity to a previous assessment. Dynamic investigator global evaluation could catch the sufferer's progress as a result of "severe" to "moderate" in the beginning (15,16).

Table 2: Static IGA/PGA scale description (adopted from Langley et al. (16))

Score	Brief description	Explanation
0	Clear	There is no plaque level
1	Minimal	Plaque level is kept to a minimum
2	Mild	Plaque development is mild
3	Moderate	Plaque grade is moderate
4	Definite	Modest plaque rise
5	Severe	Severe plaque rise

In earlier studies, a four-point severity scale was employed. Across most versions, physicians graded illness severity using a six-point or seven-point scale of "cleared" to "serious" or "extremely severe". However, different investigator global evaluations or physician global assessments use diverse explanations for every single point number (for example, a score of 1 may signify "minimum"/ "nearly clear"), as well as the assessment standards for each descriptor change. No physician assessment style is documented as a standard measure, and experts and regulatory authorities have yet to agree on scale definitions/descriptors (16).

The “rule of ten” for Psoriasis Severity Measurement

The "rule of ten" is one of the most widely recognized, owing to its simplicity and ease of usage. According to guidelines of the American Academy od Dermatology, individuals with BSA, PASI and DLQI scores less than 10 have mild to moderate psoriasis, and those with findings more than 10 have moderate to severe psoriasis. This classification is doubtful since it employs arbitrary thresholds to prevent under-treatment in minor PASI cases. It includes specific locations, including the hand plantar or face, which causes a significant sickness burden. However, systemic biological treatment will be limited to people with moderate-to-severe psoriasis (17).

Dermatology Life Quality Index (DLQI) is an independent tool that assesses whether psoriasis and other skin disorders impair a patient's quality of life (QoL). It consists of ten questions covering six dimensions of QoL, including symptoms and emotions, daily activities, entertainment, employment, personal ties, and treatment, with findings yielding a value ranging from 0 to 30 (Maximum impact on QoL) (14).

1.2.3. Psoriasis with Comorbidities

Psoriasis as a systemic inflammatory disease is linked to a higher incidence of comorbidities, including hypertension, hyperlipidemia, inflammatory arthritis, cancer, obesity, inflammatory bowel disease, cardiovascular events, etc. When planing a treatment plan for psoriasis patients, it is crucial to consider the unique characteristics of each patient, as these comorbidities frequently influence the choice between different therapies (18).

Psoriatic Arthritis: Psoriatic arthritis (PsA) affects over 30% of people with psoriasis. Psoriatic arthritis can affect joints in the body, from major joints like the elbows and knees to minor joints like the toes and fingers, the spinal, and even the sacroiliac joints. It is progressive, causing the affected joints to become swollen and painful, culminating in oligoarticular or polyarticular arthritis, reducing mobility or, in extreme cases, joint destruction and deformity. It is crucial to remember that the rheumatoid factor blood test is often negative. Soft tissue swelling, various levels of joint degradations, joint space shortening, and osseous overgrowth, comprising periarticular and shaft periostitis and osteolysis, are X-ray characteristics of PsA. Nail psoriasis affects up to 90% of people with PsA (6).

Psoriasis with Metabolic Syndrome: Metabolic problems, particularly metabolic syndrome, are usually related to moderate to severe psoriasis (6).

Psoriasis with Cardiovascular (CV) Disease: Psoriasis is one of the factors associated with heart disorders such as hypertension, hyperlipidemia, significant adverse CV events, and MI (6).

Psoriasis with Nephropathy: Psoriasis patients may suffer from renal disease or immunity-related renal problems and skin lesions. Psoriasis is a distinct disease risk for CKD and ESRD (6).

Psoriasis with Bowel Disease: Patients with IBD (Irritable Bowel Disease), as well as ulcerative colitis and Crohn's disease patients, have immune-mediated inflammation comparable to psoriasis. Psoriasis and inflammatory bowel disease have substantial bidirectional relationships (6).

Psoriasis with Brain Diseases: Psoriasis is a disease with significant emotional and psychological impact on individuals. People with psoriasis may experience depression, multiple cerebral sclerosis, or other psychological indications, as well as a considerably reduced QoL and mental load, including nervousness, sadness, and suicidal behaviour and actions (6).

Pulmonary Disease and Psoriasis: Some patients develop interstitial respiratory problems or other lung disorders (6).

Psoriasis with Liver Disease: Nonalcoholic fatty liver illness (NAFLD), liver cirrhosis, or liver function impairment are typical complications of psoriasis (6).

Psoriasis with Uveitis: Uveitis is a well-known ophthalmologic symptom of the eye. Patients with psoriasis have a dramatically elevated risk of developing uveitis (6).

Lupus Erythematosus and Psoriasis: It is uncommon for persons with psoriasis to develop lupus erythematosus, but patients with serologically confirmed lupus erythematosus have (6).

Malignancy and Psoriasis: Psoriasis is also linked to a minimal and increased threat of epidermal or internal organ tumours (6).

1.3. Causes

Psoriasis is an immune-mediated condition. The likelihood of acquiring psoriasis may also be increased by a few environmental variables (1):

- Diseases, including HIV and streptococcal bacteria.
- Smoking.
- Obesity.

Skin cells turnover cycle is turnover of basal cells to the stratum corneum and in healthy people it takes 28 days, but in psoriasis, they proliferate more than average. Due to this quick cellular proliferation, the most prevalent form of psoriasis, plaque psoriasis, develops rough, flaky spots. Psoriasis's actual aetiology is uncertain. According to researchers, genetics and ecological variables are believed to be implicated. The disease is not transmitted through a contagious route (8).

Psoriasis susceptibility-1 gene location on chromosome number 6 stayed strongly related to psoriasis, as shown by the findings of several link analyses done on huge family groups. HLA-C06 is the primary psoriasis susceptibility marker among the ten gene sites discovered on the chromosome. HLA-C 06 has fewer than half of the genetic propensity to psoriatic disease. The finding shows the occurrence of non-major histocompatibility complex susceptibility polymorphisms, which might elucidate the disease's complexity. Recent genome-wide association studies recognized more than 40 new hereditary risk factors for psoriasis. They include polymorphisms in genes implicated in skin barrier function, NF-kappa B signalling pathways, and immune responses mediated by CD8+ lymph. Even though these DNA variants encode proteins that indicate epistasis in biology, the commonly identified various-shaped variants are associated

with psoriasis possibility alone. Compared with HLA-C 06 separately, the impact explains just a small portion of the complexity of psoriasis genetics (19).

1.4. Symptoms and Signs

Common psoriasis symptoms and indicators include (20):

- Patchy outbreaks that vary widely among individuals, from small, dandruff-like flaking to extensive areas covering a significant area of the body.
- On lighter skin, lesions may appear red or pink with a silvery scale; on darker skin, they might look darker, with purple or gray undertones
- Possibly bleeding skin due to dryness and cracking
- Inflammation, burning, or pain
- Recurring skin conditions that appear for a few weeks or months before going away.

1.5. Diagnosis

The diagnosis is made by clinical examination which can include physical examination, biopsy, blood tests and questionnaires. Psoriasis has been divided into several clinical phenotypes depending on the appearance of the cutaneous patches and anatomical sites (21).

Chronic plaque psoriasis is the most prevalent type, affecting eighty to ninety per cent of all cases. Classic plaque psoriasis characterizes demarcated, symmetric, and erythematous plaque. Plaques are usually found on the scalp, chest, buttocks and extremities, although they may present anywhere on the body. Patients may have nail involvement without the presence of concurrent plaques. Itchy or painful lesions are common in active disease. Psoriasis can sometimes manifest on formerly healthy skin that has been traumatized or injured where new lesions appear. Inverse, pustular, guttate, erythrodermic, and annular psoriasis are less frequent psoriasis variations. Morphology distinguishes these variations from the usual plaque type (22).

1.6. Treatment

Many factors influence treatment selection. The prior factors include period of onset, duration, degree of illness, lesions location, patient's age, category of psoriasis, pregnancy, infection (particularly TB and serum hepatitis)/ no infection, either having health insurance coverage, previous treatment history, in addition, patient willingness to treatment. The latter comprises the drug's effectiveness, security, cost, reaction period, tolerance, occurrence, and resistance (6). There are several effective treatment for psoriasis (Figure 1) (22).

Psoriasis therapies aim to clear out scales and rapid growth of cutaneous cells (23). Topical treatment seems to be the standard treatment method for treating mild to severe illnesses. Topical treatment, which may be started in primary care, would assist most patients. Suppose topical medications do not respond satisfactorily or are impractical because of afflicted BSA. In that case, patients may be sent to a dermatologist for evaluation, where systemic with topical treatment might be prescribed (22).

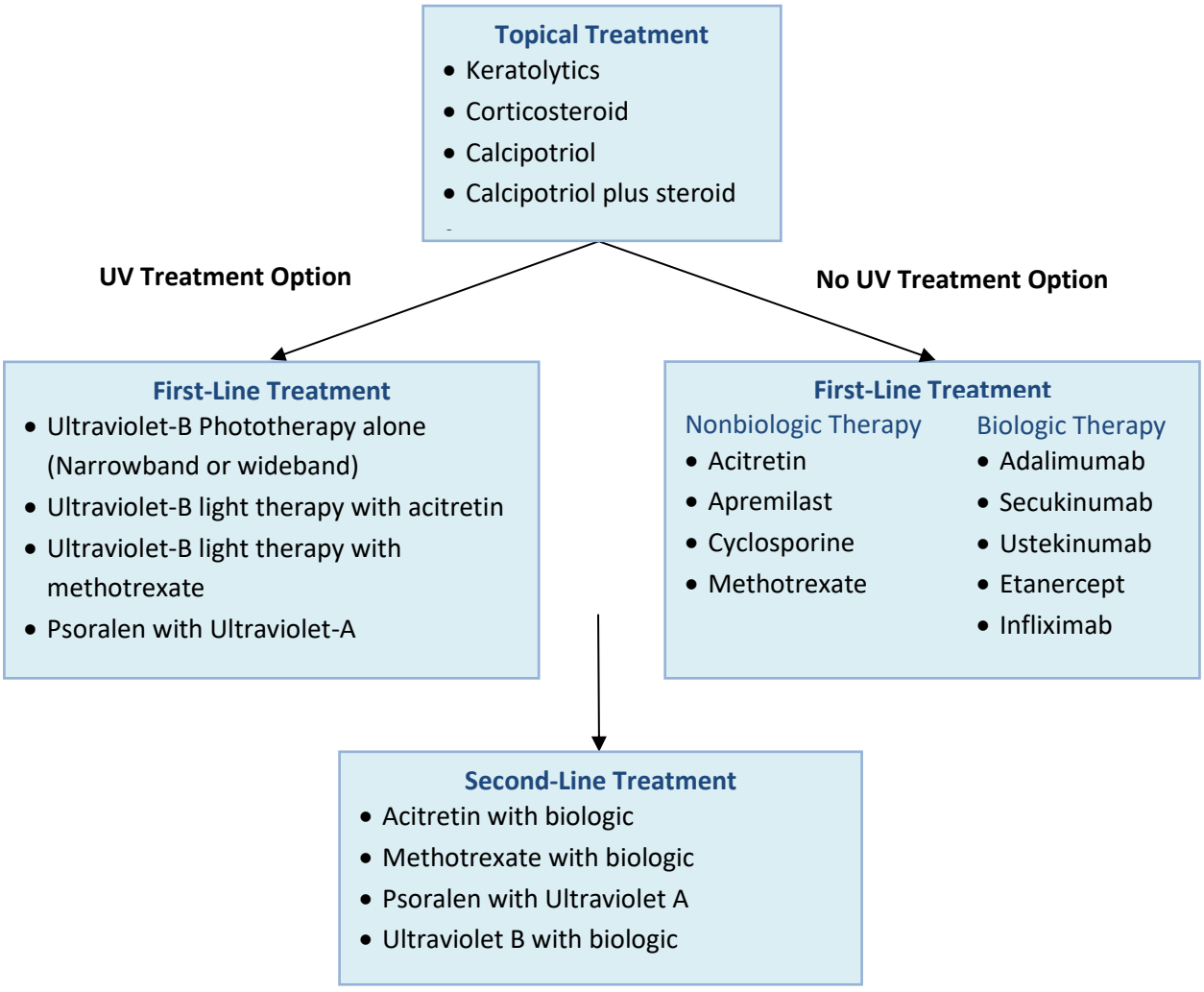

Figure 1: Treatment pattern for healthy adults with chronic plaque psoriasis (22)

Biological treatments are used for moderate to severe kind of psoriasis. Biologics target particular molecules associated with psoriasis aetiology, including TNF, IL 12, IL 17, and IL-23 (6).

Other treatments comprise oral medications and injections, phototherapy and ointments. The severity of psoriasis, how the patient respond to previous treatments and self-care techniques may decide the type of treatments that should be employed, where treatment has to adjust to the specific patient's requirements (23).

1.6.1. Topical Treatment

Patients with minor to moderate illness are frequently treated with creams, ointments, lotions, foams, or solutions, especially corticosteroids. Anthralin, retinoids, coal tar, and vitamin D-based medications are among more topical treatments (22,23).

Corticosteroids are the most commonly given topicals for mild to moderate psoriasis. On the market there are various pharmaceutical forms such as ointments, creams, oils, gels, foams, sprays, lotions, and bathes. In order to treat extensive patches and sensitive regions like the face or skin layers, mild corticosteroid ointments (hydrocortisone) are typically advised. Triamcinolone or clobetasol are potent corticosteroid creams or ointments that can be recommended for more minor, less reactive, or difficult-to-treat lesions. The skin can become thinner by prolonged usage or misuse of potent corticosteroids. Topical corticosteroids may lose their effectiveness over time (22,23).

Analogues of vitamin D3: Vitamin D3 analogues, including calcipotriol, are presented as a topical therapy in plaque psoriasis or scalp moderate to severe psoriasis. This drug alleviates symptoms by suppressing T-cell activity, altering skin cells, and multiplication and differentiating one cell. Numerous RCT studies indicated that calcipotriol is an excellent, effective option for people with moderate psoriatic plaques and is not inferior to corticosteroids in terms of effectiveness (22).

Retinoids: Tazarotene is offered as a gel or cream. It is administered once or twice daily. Skin inflammation and incresed light sensitivity are the most frequent adverse effects. Tazarotene is contraindicated during pregnancy, breastfeeding or when women are attempting to conceive (23).

Calcineurin inhibitors Tacrolimus and pimecrolimus reduce the outbreak and decrease keratinocyte proliferation. These could be particularly beneficial in places with delicate skin, like the area close to the eyes, where retinoids or hormone (e.g. steroid) containing lotions might irritate/ injure the skin. These should not be used by pregnant women, breastfeeding, or when planning a pregnancy. The prospective elevated risk of lymphoma and skin cancer makes this medication unsuitable for prolonged usage (23).

Salicylic acid: Scalp treatments using salicylic acid decrease scaling. They come in both non-prescription and pharmaceutical doses. Due to its ability to prepare the scalp for medication administration, this kind of product can be used alone or in conjunction with other topical treatments (23).

Coal tar can help to decrease scaling, irritation, and swelling. It is available in many forms, including shampoo, lotion, and oil. These can potentially cause skin irritation (23).
Anthralin proliferation of skin cells. Additionally, it helps make skin smoother and reduces scales. It should not be applied over the face or genitalia (23).

1.6.2. Orally and Parenteral Administered Treatments

Patients who have moderate or severe psoriasis mostly use orally and parenteral administered treatments. There are several potential treatments such as retinoids, cyclosporine and methotrexate. Choosing the best treatment depends on patients severity of psoriasis, blood tests and respond to previous therapy. If these therapy doesn't show effect on psoriasis treatment it is indicated to start treatment with biologic therapy such as ustekinumab, ixekizumab, secukinumab, infliximab, etanercept, guselkumab and tildrakizumab. Three of them are authorized for children: etanercept, ixekizumab and ustekinumab (22–24).

1.6.3. Phototherapy

Phototherapy is an important treatment option for severe to moderate psoriasis, mainly when topical treatments are ineffective. It comes in psoralen with ultraviolet A, broadband ultraviolet B, and narrowband ultraviolet B formulations. Because of the effectiveness and safety benefits demonstrated in several RCTs, narrowband Ultraviolet B treatment is frequently utilized. Indeed, practically any individual, especially kids and pregnant women can benefit from narrowband ultraviolet B treatment. This does not indicate that narrowband Ultraviolet B exposure raises the chances of developing cutaneous cancer. Despite its safety, the restricted accessibility of light therapy centres and requirements for regular visits, which could be three times a week for three months in starting, make it exceedingly unpleasant for sufferers (22).

1.7. Complications and Comorbidities of Moderate and Severe Psoriasis

Psoriasis patients can develop other conditions that are discussed earlier, such as psoriatic arthritis, temporary skin colour alters, i.e. post-inflammatory hypopigmentation/ hyperpigmentation, eye problems, weight gain, diabetes type 2, hypertension, heart diseases, some more immune-mediated illnesses such as gluten-sensitive enteropathy, induration, inflammatory bowel disease & mental health conditions, such as nervousness, depression (8).

Research demonstrates that "psoriasis patients had a greater prevalence of cardiovascular illnesses, overweight, sugar, high BP, high cholesterol, dysmetabolic syndrome, nonalcoholic fatty-liver problem, any malignancy, nervousness and sadness, and intestinal inflammation" (25).

A further review study revealed there is a long list of illnesses linked with psoriasis, varying from infertility to asthma symptoms. However, metabolic syndrome or its aspects such as/ weight gain, atherogenic dyslipidemia, systemic high blood pressure, or insulin resistance, heart disease, and nonalcoholic steatohepatitis are the most prevalent comorbid diseases associated with psoriasis (26).

People with moderate to severe psoriasis must work closely with their healthcare provider to manage their condition and monitor for potential complications or comorbidities.

1.8. Prevention and Management of Moderate and Severe Psoriasis

Preventing and managing moderate and severe psoriasis involves a combination of lifestyle changes, medications, and therapies (24,27,28). These are some significant approaches:

Lifestyle changes: Having a diverse diet, keeping a healthy weight, decreasing stress, and eliminating triggers such as alcohol and smoking can help prevent and manage psoriasis.

While mainly compared to standard treatment, a healthy diet could minimize the extent of psoriasis (substandard findings) and likely enhance life quality but also decrease body fat percentage (evidence-based findings). In contrast, a combined eating plan and workout routine possibly improve the extent of psoriasis and body mass index (evidence-based findings) (27).

Apart from weight gain, sedentary lifestyles, including heavy alcohol use, tobacco, and low physical activity, have been linked to the formation and exacerbation of psoriasis (29). Stress and sleep deprivation are also linked to psoriasis exacerbation (30,31). The mechanism behind the association between stress and psoriasis aggravation is unknown. However, it may comprise

neurogenic inflammation, changes within the neuroendocrine system, and white blood cell redirection to the dermis (32).

Medications: As concisely discussed in the treatment section, drugs applied to the skin, like vitamin-D analogues, corticosteroids, and retinoids, can be effective for mild to moderate psoriasis (22,23). For more severe cases, systemic medications such as biologics including adalimumab, apremilast, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, guselkumab, and tildrakizumab, and nonbiologic treatment including methotrexate, acitretin, cyclosporine may be necessary (6,22,23,27). Here, we will go through a few biologics and nonbiologic agents.

Nonbiologic medications:

Acitretin: An oral retinoid, acitretin is a derivative of vitamin A. Acitretin's mode of action is not comprehended. It contains anti-inflammatory and immunomodulatory properties and modulates cutaneous differentiation and proliferation. Despite other systemic psoriasis medications, acitretin does not inhibit the immune system (27).

Acitretin treats psoriasis in dosages of 10-50 mg per day. A combination of acitretin with phototherapy is more effective than one therapy alone. The combined treatment assists in minimizing long-term harmful effects and reduces phototherapy's cumulative dosages, frequency, and duration (27).

Teratogenicity is the most serious safety issue with acitretin treatment when administered in women of reproductive age. This drug is not safe to use while pregnant (27).

Mucocutaneous side effects include xerosis, eye dryness, nose or oral epithelium, epistaxis, cheilitis, itchy/ burned skin, and brittle nails, which can range from moderate to severe according to specific sufferer features and acitretin dosage. Women have increased hair loss. Patients should be continuously watched after starting medication to avoid significant side effects (27).

Cyclosporine: The drug is a powerful immuno-suppressive agent that works by binding to cyclophilin (a protein), inhibiting calcineurin and blocking proinflammatory signals. Therefore, many inflammatory mediators, including interferon and IL-2, are lowered, resulting in decreased T-cell activation. This rug is not utilised as a long-term therapy for psoriasis due to an extensive list of potentially dangerous side effects. However, it is helpful as a fast-acting drug for severe, resistant illness, abrupt flaring, and erythroderma. It may also be a primary therapy for better long-term care (27).

Many experts recommend starting cyclosporine therapy for psoriasis with a medium dosage of 2.5-3 mg/daily administered two times daily for four weeks before increasing the dosage by 0.5 mg per kg per day until satisfactory stability is attained. This strategy may be preferable for mild illness and detecting harmful effects when the dose is raised. On the other hand, patients with severe illness who require quick improvement can be started on a dosage of approximately 5 mg per kg per day and then decreased after progress is observed (27). Cyclosporine's most prevalent side effects include renal toxicity and high blood pressure (27).

Cyclosporine should be used with caution in geriatric, pregnant, or immunocompromised individuals. A background of systemic malignancy, renal disease, high blood pressure, past psoralen with ultraviolet-A therapy, persistent infectious diseases, and intolerance to cyclosporine are all contraindications to this medication. Cyclosporine should also be used with caution in patients who are taking other drugs that may interact with cytochrome-P3A4. Live vaccines are also not recommended for persons taking cyclosporine (27).

Cyclosporine must not be recommended in individuals who are in poor health or who have potential risks for serious side effects (27).

Methotrexate: Methotrexate has been utilized to treat psoriasis for almost four decades. Low-dose methotrexate, i.e., less than 25 mg per week, reduces lymphoid cell proliferation, and this direct immunosuppression impact is assumed to be the mechanism through which this drug reduces psoriatic illness (27).

It is usually given in doses ranging between 7.5-25mg per week, in one or three dosages spread over twenty-four hours. In a validity testing research, 10 mg weekly dose was shown to be delayed responding as 25 mg weekly treatment, but with less severe adverse reactions. Daily treatment of 2.5 mg six days a week had less benefit than a weekly dosage of 15 mg in three doses every eight hours for 24 hr. while being most probable to cause an increase in hepatic enzymes (27).

Long-term methotrexate users require regular testing to track blood levels and liver health. It must be stopped at least three months before trying to get pregnant. It is not advised for breastfeeding mothers to take this medication (23).

Biologics: Table 3 (29) shows the target of different biologics. This study describes a few biologics in particular that are listed further down.

Table 3: The drug's targeted location and action (adopted from Kamata et al. (33))

Drug entity	Action/ Site
Adalimumab **Infliximab** **Etanercept** **Certolizumab-pegol** **Golimumab**	TNF-α blockage
Ustekinumab	IL-12/23 blockade
Guselkumab **Risankizumab**	IL-23 blockade
Brodalumab **Secukinumab** **Ixekizumab**	IL-17 blockade
Abatacept	CTLA4-Ig

Adalimumab: Traditionally, the disease-modifying antirheumatic medications (DMARD) used to treat rheumatoid arthritis were used to manage mild to severe psoriasis. Adalimumab is an entirely human anti-TNF monoclonal antibody that relieves both dermatological and joint symptoms, reduces disability caused by joint deterioration, and can enhance wellbeing QoL while usually tolerated well (34,35). This medication exhibited excellent outcomes for persistent plaque psoriasis and appears to be a potential therapeutic option for people with severe to moderate plaque psoriasis (34).

The suggested dose for psoriasis treatment is 80 mg, which is continued with 40 mg once every two weeks (34).

Infection of the upper respiratory tract, acute rhinitis, migraine, injection site responses, and other dangerous infections are the most prevalent adverse effects of adalimumab therapy. Because the mechanism of action of adalimumab may reduce the human body's defences against pathogens and cancers, these risks are the most serious when taking this type of drug (34).

Guselkumab: Guselkumab is prescribed for adults with moderate to severe plaque psoriasis that is not unsuitable for systemic or light therapy (UV radiation therapy). It is unknown whether guselkumab is harmless and efficient in kids aged 18 or below. Guselkumab is the first and only FDA-approved biological treatment that targets just interleukin-23 (IL-23), a cytokine involved in plaque psoriasis (36).

Guselkumab is given as an SC injection in a suggested dose of 100 mg at week zero, week four, and every eight weeks after that (36).

The most frequent side events observed are upper respiratory tract infections, headaches, injection site responses, arthralgia, diarrhoea, gastroenteritis, and increased infection risk. Guselkumab is not recommended for use in patients who have an illness which neither goes away nor returns, who have or have been in intimate interaction with an individual suffering from tuberculosis, who have recently had or are due to get a vaccination, who plan to become pregnant, or who are nursing. Guselkumab seems promising for plaque psoriasis, but further research is needed to determine its long-term safety and effectiveness (36).

Ustekinumab: Ustekinumab is a medication which is employed to treat moderate-to-severe psoriasis. It is a humanized-monoclonal-antibody which prevents the production of IL-12 and IL-23. It is beneficial in the treatment of chronic plaque psoriasis as well as other types of psoriasis, such as nail psoriasis, erythrodermic psoriasis, generalized pustular psoriasis, and palmoplantar pustulosis, and it also treats Crohn's disease (37).

Ustekinumab is given by subcutaneous injection. The dosage is 45 mg for people weighing less than 100 kg, and 90 mg for patients weighing more than 100 kg. A second dosage is administered four weeks following the initial injection, and subsequent doses are administered every 12 weeks (37).

Adverse events due to ustekinumab include injection site reactions, infections, malignancies and immune system disorders. Ustekinumab ought not to be given to individuals with a record of recurrent infection or active tuberculosis prior to biological treatment. Patients taking biological drugs should undergo regular blood testing every six months, including a complete blood count and liver enzyme testing. TB tests should be done regularly (37).

Brodalumab: Brodalumab is a recombinant, completely humanized-monoclonal-antibody which binds to IL-17 receptor A (IL-17R) with strong affinity. It is active in treating moderate and severe persistent psoriasis plaque. It is a highly effective psoriasis medication with a mode of action distinct from previous IL-17-targeting therapies (38).

Brodalumab is prescribed as 140 mg or 210 mg SC injections at weeks 0, 1, and 2 and then every two weeks afterwards (38,39). Brodalumab is recommended for individuals who require quick disease management and have no previous depressive disorders or suicidal thoughts (38).

Alternative therapies: Natural remedies such as aloe vera, fish oil, turmeric, may help in managing symptoms for some people who are suffering from psoriasis (28).

Emotional support: Living with psoriasis can be stressful, and seeking emotional support from friends, family, or a mental health professional can be beneficial (40).

People with psoriasis should have frequent follow-ups with their doctor to evaluate their condition and assess any possible complications or comorbidities. Managing psoriasis requires a comprehensive approach, and treatment plans should be tailored to each individual's needs. With proper care and management, it is possible to control psoriasis symptoms and improve the overall quality of life.

1.9. Pharmacoeconomic Aspects

Psoriasis can be a costly disease to manage in relation to direct and indirect medical expenses (41,42). Direct costs include expenses related to therapeutic management, like clinician visits, medications, and hospitalizations. The indirect costs involve loss of production due to missed workdays, reduced productivity at work, or decreased quality of life (42). Some pharmacoeconomic aspects of psoriasis are as follows:

1.9.1. Cost of Illness

The cost of illness in psoriasis includes direct and indirect costs (41,42). According to research published in the Journal of the American Medical Association (JAMA) Dermatology, the yearly cost of psoriasis in the United States in 2013 ranged from $112 billion to $135 billion (43). This cost includes up to $63.2 billion in direct expenditures (related costs incurred as a result of underlying conditions) and $35.4 billion in indirect costs (as measured by a decrease in job productivity) (41).

Research studies discovered that employees with severe psoriasis use sick leave for 2.3 - 26 days of work each year (44). According to the US National Psoriasis Association, psoriasis patients miss 56 million work hours annually, which can result in lost wages and reduced productivity (45).

According to the American Journal of Managed Care, the yearly medical cost of psoriasis treatment is projected to be $35.2 billion, including $12.2 billion in direct expenses and $23 billion in indirect costs (associated with decreased wellness-related QoL and productivity loss) (46).

Overall, the cost of illness in psoriasis can be substantial, both for individual patients and society. Effective disease management can help reduce the financial burden and improve the QoL for patients.

1.9.2. Cost of Treatment

The cost of psoriasis treatment can vary widely based on the severity of the disease and the specific treatment used (46). Some medications used to treat psoriasis, such as biologics, can be expensive (47).

A study showed that ustekinumab ($53,909) had the highest cost for a year of initiation and maintaining therapy, followed by etanercept ($46,395) and adalimumab ($39,041). Ustekinumab ($25,012) had the highest sales-based cost, followed by adalimumab ($6,786) and then etanercept ($6,629). Sales-based costs climbed by 20% on average every year (47).

Table 4: Annual expenses for psoriasis treatment using biologics (adopted from Cheng et al.(47))

Drug	**Initial Dosing**	**Average wholesale price (2014 USD)**	**Initial followed by maintenance (USD)**	**Maintenance (USD)**
Etanercept	50 mg two times a week for three months, next 50 mg weekly	15.47/ mg	46,395	37,111
Adalimumab	The maintenance dosage is 40 mg weekly after the initial dose of 80 mg.	46.92/ mg	39,041	36,038
Ustekinumab	Considering a weight of 100kg: 45mg at 0 and 4-week intervals, continuing every 12 weeks afterwards.	196.63/ mg	53,909	44,924

Patient adherence: Medication adherence is essential in achieving positive outcomes and minimizing costs associated with psoriasis treatment (48,49). Non-adherence can increase healthcare costs and decrease treatment effectiveness (49).

1.9.3. Cost-effectiveness & Cost-benefit Analysis

A cost-effectiveness enquiry relates two medicines, one that is more expensive and more effective and another less expensive. Cost-benefit investigation is identical to cost-effectiveness analysis, excluding the advantages of health care interventions are expressed in monetary terms (50). The cost-effectiveness of psoriasis treatments is essential in healthcare decision-making (51).

Cost-benefit cost-effectiveness is contingent on the treatment's cost, effectiveness, and utility (50) and depends on the treatment efficacy and side effect profiles.

An effective intervention increases happiness and health in a suitable for a disease treatment. The cost, effectiveness, and efficiency of mutually exclusive techniques in producing desired benefits are all compared in a cost-effectiveness analysis (CEA), one type of economic review (52). Finding the treatment that produces the most significant benefit against disease at a reasonable degree of efficiency is the aim of cost-effectiveness. Quality-adjusted life years (QALYs) are a common unit of measurement for effectiveness; however, depending on the decision-maker's objectives, life years, infections/cases prevented, or other measures of benefit may be more appropriate (53). Costs include any necessary upstream costs and the price of implementing the strategy. Depending on the analysis's point of view, it is decided which costs to include.

A cohort study conducted in public hospitals in Malaysia evaluated the affordability of three regimens for moderate and severe psoriasis treatment, i.e. light therapy with topical, systemic with topical, and biologics with topical medication. Topical and systemic regimens were discovered to be the most cost-effective therapy at the most affordable price, i.e. US$2582.55 (RM9034.56), followed by topical and phototherapy valued US$8026.93 (RM28 080.71), and topical and biologic, valued US$15 518.06 (RM54 287.02), showed in Table 5 (51).

Table 5: Expenses and cost-effectiveness for psoriasis management (adopted from Azizam et al. (51))

Treatment Regimen	**Per Patient Cost (Malaysian Ringgit)**	**Total Treatment Cost (Malaysian Ringgit)**	**Effectiveness % (n)**	**Cost-Effectiveness * (Malaysian Ringgit)**	**Cost-Effectiveness (USD)**
Systemic with topical	4969.01	298 140.44	55.0 (33/60)	9034.56	2582.55
Phototherapy with topical	12 480.32	224 645.68	44.4 (8/18)	28 080.71	8026.93
Biologics with topical	36 191.35	434 296.15	67.7 (8/12)	54 287.02	15 518.06
Total	**10 634.25**	**957 082.27**			

*Cost effectiveness = total treatment cost/ patients number (n) obtained PASI seventy-five and/or BSA less than five and/or DLQI less than or equal to five

1.9.4. Cost-utility Analysis

It is a tool for determining the cost-effectiveness of treatment options. It entails weighing the cost of various treatment alternatives against their health outcomes, which are determined by quality-adjusted life years (QALYs) (54).

In psoriasis treatment, CUA can be used to compare the cost-effectiveness of topical creams, phototherapy, systemic medications, and biological agents. The cost of each treatment option is compared with the improvement in QALYs that it provides.

Australian research issued in Journal of The American Academy of Dermatology (JAAD) showed adalimumab, etanercept, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, as well as ustekinumab were compared by way of preferred therapies in people who have severe and prolonged psoriasis plaque in this cost-utility study. The best cost-effective preferred treatment was a biologic route that began with tildrakizumab (AUD 39 930; total value of 1.568 QALYs ended ninety-six weeks). Compared to preferred tildrakizumab,

preferred secukinumab and risankizumab exhibited additional cost ratios of AUD 194 524/QALY and AUD 479 834/QALY, respectively (55).

Table 6: Total cost and QALYS for biologic drugs in the baseline (adopted from Sun et al. (55))

Drugs	**Baseline Effectiveness (QALYS)**	**Cost (AUD)**	**Incremental cost-utility ratio related to Tildrakizumab (AUD/ QALY)**
Adalimumab	1.554	42 384	─172 379 (captivated)
Etanercept	1.538	45 602	─192 307 (captivated)
Guselkumab	1.584	49 720	607 746 (captivated)
Ixekizumab	1.581	48 635	674 829 (captivated)
Risankizumab	1.587	49 084	479 834 (Not captivated)
Secukinumab	1.582	42 696	194 524 (Not captivated))
Tildrakizumab	1.568	39 930	Nill
Ustekinumab	1.558	44 924	─492,183 (captivated)

The pharmacoeconomic analysis is a crucial tool for evaluating the cost-effectiveness of psoriasis treatments. It can help healthcare providers and policymakers create appropriate choices regarding treatment alternatives, which can ultimately improve patient outcomes and reduce healthcare costs.

1.9.5. Net Monetary Benefit

Net monetary benefit (NMB) serves as a concise measure expressing the value of an intervention in monetary terms, given a known willingness-to-pay (WTP) threshold for a unit of benefit (56). Net Monetary Benefit (NMB) can be used to assess clinical prediction models, in which a cut point, also known as a probability threshold, is used to generate predicted classes rather than probabilities; it can apply to prognostic models. Even though providing the user with a predicted chance is often advantageous in clinical situations, it could also be helpful to model the outcome of the choice that results from this likelihood (57). For instance, the current study aims to define the probability threshold for a clinical prediction model that forecasts falls in patients with psoriasis. This threshold is recommended by best practices to prioritise fall prevention interventions over no therapy at all. Before implementation, researchers can evaluate the model's influence and the suggested threshold by calculating the NMB of these choices.

2. HYPOTHESIS

Using ustekinumab in the treatment of severe and moderate psoriasis shows non-inferiority compared to acitretin using a comparative effectiveness research method to show that a less costly medication is not worse than the current standard regarding safety and/or efficacy.

The objective of a non-inferiority trial is to show that ustekinumab is not worse than acitretin by more than 15% calculated by a one-sided CI as regards the quality of life of patients with psoriasis treated with ustekinumab as compared to patients treated with acitretin.

3. AIMS AND PURPOSE OF THE RESEARCH

3.1. General Aim

The general aim of this research is to evaluate direct cost of treatment of moderate and severe psoriasis with ustekinumab as a new drug treatment compared to acitretin.

3.2. Specific Aim

Specific aims are to investigate whether ustekinumab increases the quality of life compared to acitretin and to show that the quality of life of patients who received biological treatment increases faster than the quality of life of patients on other systematic therapies.

4. METHODS

4.1. Study Design and Data Sources

In this retrospective study, data were collected at the "Sestre milosrdnice" Clinical Hospital Center from patients diagnosed with moderate to severe psoriasis who received treatment with ustekinumab. The comparative group consisted of patients with confirmed moderate to severe psoriasis who were treated with acitretin. All patients were above 18 years of age, and ethical approval was obtained from the "Sestre milosrdnice" Clinical Hospital Centre Ethics Committee.

The inclusion criteria encompassed patients diagnosed with moderate to severe psoriasis without concurrent diseases that could impact their Dermatology Life Quality Index (DLQI), Psoriasis Area and Severity Index (PASI) or Body Surface Area (BSA) scores who were treated with either ustekinumab or acitretin. Exclusion criteria involved patients with other diseases potentially influencing their DLQI, PASI, or BSA scores and patients who did not receive acitretin or ustekinumab in their treatment regimen. All data were collected from patients' medical records. Collected data included general demographic characteristics, such as age and gender. Disease severity was assessed using PASI scores, body surface area involvement was measured using BSA scores, and quality of life was evaluated through DLQI questionnaire results. All outcomes were monitored at treatment initiation, 12 weeks, and 52 weeks after the initial drug administration. Additionally, data were collected on the type and number of laboratory tests conducted before treatment initiation and during therapy, the total number of dermatologist visits during the observation period, and other therapies used alongside the investigational drugs for psoriasis treatment. The costs of laboratory tests, dermatological examinations, and therapies were derived from data provided by the Croatian Institute for Health Insurance.

A total of 25 patients who received ustekinumab and 42 patients who received acitretin were included in this research.

4.2. Statistical Analysis

For calculation, average, mean, median and standard deviation, Microsoft Excel v.2309 was used. Changes in Psoriasis Area and Severity Index, Body Surface Area, and Dermatology Life Quality Index from baseline to weeks 12 and 52 were determined using an independent means t-test. If $p<0,05$, we concluded there is a statistically significant difference. Noninferiority is a situation where the difference between the means is not less than -15,0. The 95% confidence bound satisfies the constraint using a one-sided confidence interval (CI). All calculations were made using R 4.3.3.

For calculating the quality-adjusted life year (QALY), the "QALY" 0.1.0.9000 V package by Nathan Green was performed using R software 4.3.3. using the following formula (58).

$$\sum interval(i) * utility(i) * QoL(age(i)) * discount(i)$$

for i = 1, ..., time_horizon

One-Way ANOVA was used to determine the difference between total QALYs gained by psoriasis patients using treatment acitretin, ustekinumab (45 mg), and ustekinumab (90 mg).

A cost-effective and net monetary benefit model was performed using R studio 4.3.3. to evaluate the costs, benefits, cost-effectiveness and net monetary benefit of treatments acitretin, ustekinumab 45 mg, and ustekinumab 90 mg for different costs by measuring various psoriasis index (PASI, BSA, and DQLI) in psoriasis patients of various age groups at treatment start, after 12 and 52-weeks of treatment. Based on the literature, Willingness to pay (WTP) was taken as three times Gross Domestic Product (GDP), which for Croatia is calculated at 50258 euro.

5. RESULTS

In total, 25 patients using ustekinumab and 42 patients using acitretin, prescribed as the first oral treatment for psoriasis, were analysed. Changes in DLQI, PSAI and BSA were followed during 52 weeks. Because of earlier discontinuation using acitretin due to side effects and/or worsened laboratory values, 13 patients were not included in the study. Overall, 28 patients using acitretin were considered for this study. In the group of patients using ustekinumab, there were 17 males and eight females, with an average of 42 years old and a range of 19-67 years. The patients using acitretin were 14 males and 13 females, with an average age of 53,81 years and a range of 37-77 years (Table 7).

Table 7. Distribution of patients using acitretin and ustekinumab

	Acitretin	**Ustekinumab**
Female	13	8
Male	14	17
Total	27	25
Average years	53.81	42.04
Standard deviation	9.77	9.71
Median	53	43
Range	37-77	19-67

Before starting the treatment with acitretin and ustekinumab, patients must undergo laboratory tests. For acitretin laboratory tests, they must do complete blood count (CBC), differential blood count (DBC), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), serum bilirubin, serum creatinine, cholesterol and triglycerides. Repeating those tests every 3 months during the whole treatment is also obligatory. Also, for women, it is necessary to have a negative pregnancy test since acitretin is proven to be teratogenic. Regarding ustekinumab, it is not necessary to do standard laboratory tests like those

for acitretin. However, it is essential to perform laboratory tests to exclude chronic latent infections in the body (serology HBV, HCV, HIV, Quantiferon test). In this research, patients did basic laboratory tests before and during using ustekinumab. Before starting ustekinumab treatment, the relevant dermatologist committee must approve its use. It is based on the non-effectiveness of previous treatment (the target values of DLQI, BSA and PASI were not achieved). Price of examination and laboratory tests are shown in table 8. The average cost per patient per year of treatment (direct cost) is shown in table 9.

Table 8. Prices of examination and laboratory tests

Treatment	Cost in euros (€)
First dermatologist examination	12.63
Control dermatologist examination	8.32
Team consultation (at least three experts in a group)	16.59
Complete blood count (CBC)	19.56
Differential blood count (DBC)	30.66
Aspartate transaminase (AST)	6.13
Alanine transaminase (ALT)	6.13
Gamma-glutamyl transferase (GGT)	6.13
Serum bilirubin	6.13
Serum creatinine	6.13
Cholesterol	7

Triglycerides	7
Quantiferon test	235.93
HBV test	588.94
HCV test	563.64
HIV test	668.07
Ustekinumab 45 mg	2891.22
Ustekinumab 90mg	2889.93
Acitretin	39,24
Calcipotriol + betametazon (used along acitretin)	21.84
Betametazon + salicylic acid (used along acitretin)	5.44

Table 9. Average cost per patient per year of treatment (direct cost)

Acitretin	**1407.39**
Ustekinumab 45 mg	19824.93
Ustekinumab 90 mg	19817.19

In this research, BSA, DLQI, and PASI score data were obtained at the beginning of each treatment, 12 weeks after the treatment started, and 52 weeks after the treatment started. After the first evaluation of 6 weeks, the full effect of the drug acitretin is not expected. However, it is necessary to reach a full three months from the start of therapy to conclude how successful the therapy is depending on PASI, BSA and DLQI. For successful therapy, it is necessary to achieve PASI 75 and absolute DLQI 5 or less.

For ustekinumab, the first evaluation takes place after 12 weeks of therapy. Worsening can be defined as a value at DLQI >5 and PASI >10, BSA >10. The approach is individualized; not every patient's skin deterioration is the same.

Table 10 and Figure 2 demonstrate the mean change –mean and standard deviation for each treatment and each Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index (DLQI) scores and each period (start of treatment, 12 and 52- weeks after treatment). Generally, the Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index (DLQI) scores decrease over time, i.e., from the start of treatment to 52 weeks after treatment. At the beginning of the treatment, patients treated with acitretin have lower scores of Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index (DLQI) compared to those treated with ustekinumab 45 mg and 90 mg. At 52 weeks after treatment, patients treated with ustekinumab 45 mg and 90 mg had lower scores across all outcomes (Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index (DLQI)).

Table 10: Mean change in Psoriasis Area and Severity Index, Body Surface Area, and Dermatology Life Quality Index scores from baseline to weeks 12 and 54.

	Acitretin			ustekinumab 45mg			ustekinumab 90 mg		
Period	**Start of treatment**	**12 weeks after treatment**	**52 weeks after treatment**	**Start of treatment**	**12 weeks after treatment**	**52 weeks after treatment**	**Start of treatment**	**12 weeks after treatment**	**52 weeks after treatment**
Score									
PASI (Mean/SD)	11.54 ±4.28	9.10 ±4.32	6.01 ±5.30	27.30 ±15.51	5.28 ±5.40	0.79 ±1.45	31.94 ±10.99	8.01 ±4.71	1.99 ±2.02
BSA (Mean/SD)	8.55 ±3.87	6.46 ±3.43	4.30 ±4.84	31.18 ±26.8	6.41 ±5.64	1.59 ±3.18	43.38 ±23.10	22.50 ±21.69	2.50 ±4.38
DLQI (Mean/SD)	8.46 ±3.18	5.00 ±2.82	3.39 ±3.18	21.06 ±5.40	6.71 ±5.99	1.35 ±2.57	20.00 ±6.05	8.75 ±7.11	1.50 ±1.77

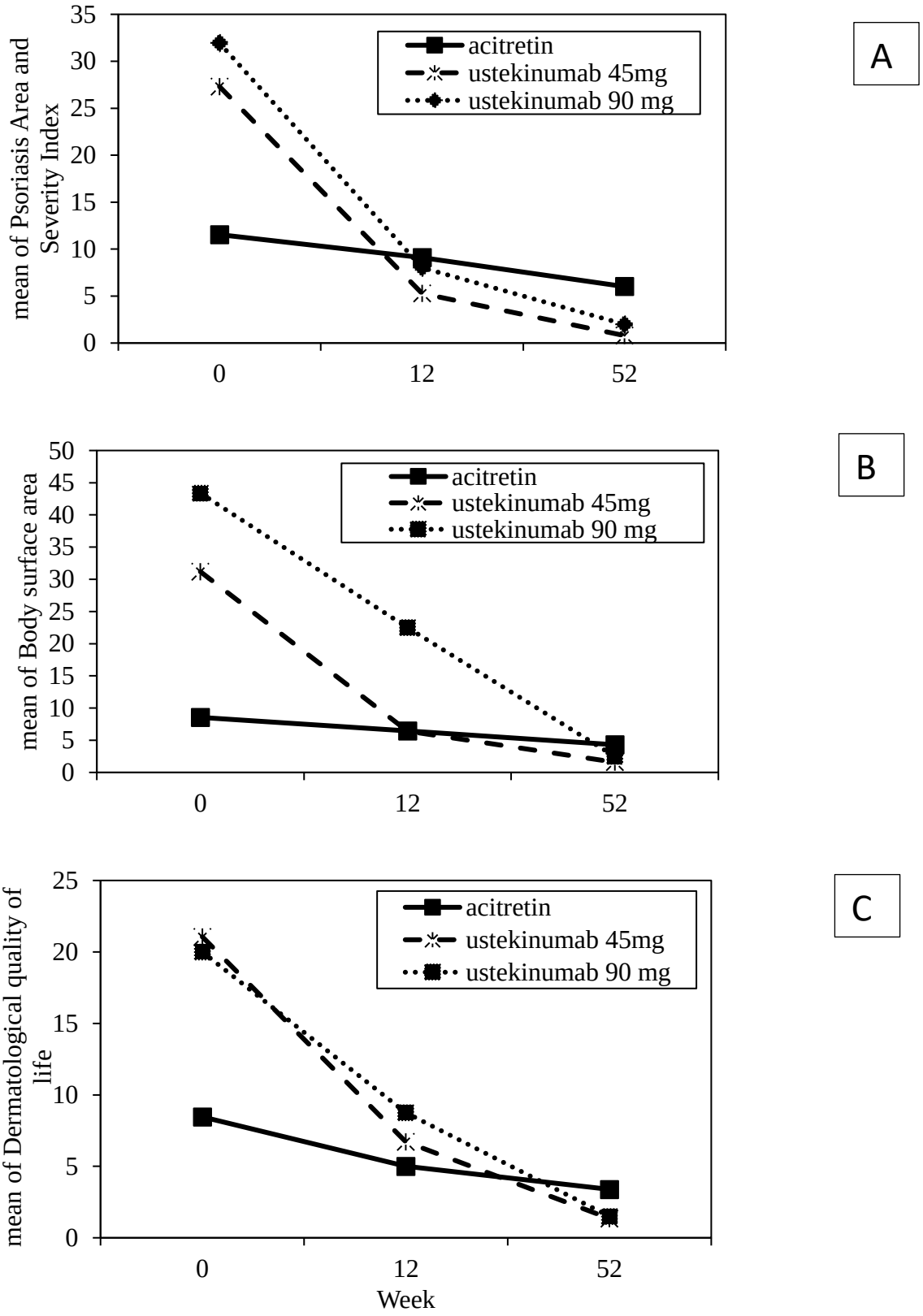

Figure 2. Mean change in Psoriasis Area and Severity Index (A), Body surface area (B), and Dermatology Life Quality Index (C) scores from baseline to weeks 12 and 52.

Table 11 summarizes the changes in Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index (DLQI) from baseline to weeks 12 and 52 using an independent means t-test. The Psoriasis Area and Severity Index scores significantly changed, on average, from baseline to week 12 ($p<0.05$) and week 52 ($p<0.05$) across all treatments. Similarly, Dermatology Life Quality Index (DLQI) scores significantly changed from baseline to week 12 ($p<0.05$) and week 52 ($p<0.05$). For Body surface area, the results were similar, except that the change from baseline to week 12 ($p=0.084$) was not significant at a 5% level. When comparing acitretin and ustekinumab (45 and 90) treatments (Table 12), at week 12, we found no significant differences in PASI, BSA and DLQI scores for patients treated with both treatments except for the PASI score for those treated with ustekinumab 45 mg. At week 52, there were significant differences in PASI, BSA and DLQI scores for patients treated with both treatments, except for the BSA score for those treated with ustekinumab 90 mg.

Figure 3 shows the results from a non-inferiority test comparing acitretin and ustekinumab (45 and 90) treatments. The results demonstrate that both ustekinumab (45 and 90) are not inferior to a standard sample treated with acitretin. Noninferiority is a situation where the difference between the means is not less than -15,0. The 95% confidence bound satisfies the constraint using a one-sided confidence interval (CI).

Table 11: Summary of change from baseline in Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index at weeks 12 and 52.

	Week 12			Week 52		
	acitretin	**ustekinumab 45**	**ustekinumab 90**	**acitretin**	**ustekinumab 45**	**ustekinumab 90**
PASI (Mean/SD)	9.10 ±4.32	5.28 ±5.40	8.01 ±4.71	6.01 ±5.30	0.79 ±1.45	1.99 ±2.02
P value	**0.038**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
BSA (Mean/SD)	6.46 ±3.43	6.41 ±5.64	22.50 ±21.69	4.30 ±4.84	1.59 ±3.18	2.50 ±4.38
P value	**0.037**	**<0.001**	0.084	**<0.001**	**<0.001**	**<0.001**
DLQI (Mean/SD)	5.00 ±2.82	6.71 ±5.99	8.75 ±7.11	3.39 ±3.18	1.35 ±2.57	1.50 ±1.77
P value	**<0.001**	**<0.001**	**0.004**	**<0.001**	**<0.001**	**<0.001**

Table 12: Comparison of acitretin and ustekinumab (45 and 90) treatment using Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index at weeks 0, 12 and 52.

	Week 0		Week 12		Week 52	
	ustekinumab 45	**ustekinumab 90**	**ustekinumab 45**	**ustekinumab 90**	**ustekinumab 45**	**ustekinumab 90**
PASI (Mean/SD)	27.30 ±15.51	31.94 ±10.99	5.28 ±5.40	8.01 ±4.71	0.79 ±1.45	1.99 ±2.02
P value	**<0.001**	**0.001**	**0.019**	0.569	**<0.001**	**0.003**
BSA (Mean/SD)	31.18 ±26.8	43.38 ±23.10	6.41 ±5.64	22.50 ±21.69	1.59 ±3.18	2.50 ±4.38
P value	**0.003**	**0.004**	0.973	0.075	**0.028**	0.335
DLQI (Mean/SD)	21.06 ±5.40	20.00 ±6.05	6.71 ±5.99	8.75 ±7.11	1.35 ±2.57	1.50 ±1.77
P value	**<0.001**	**<0.001**	0.283	0.184	**0.024**	**0.041**

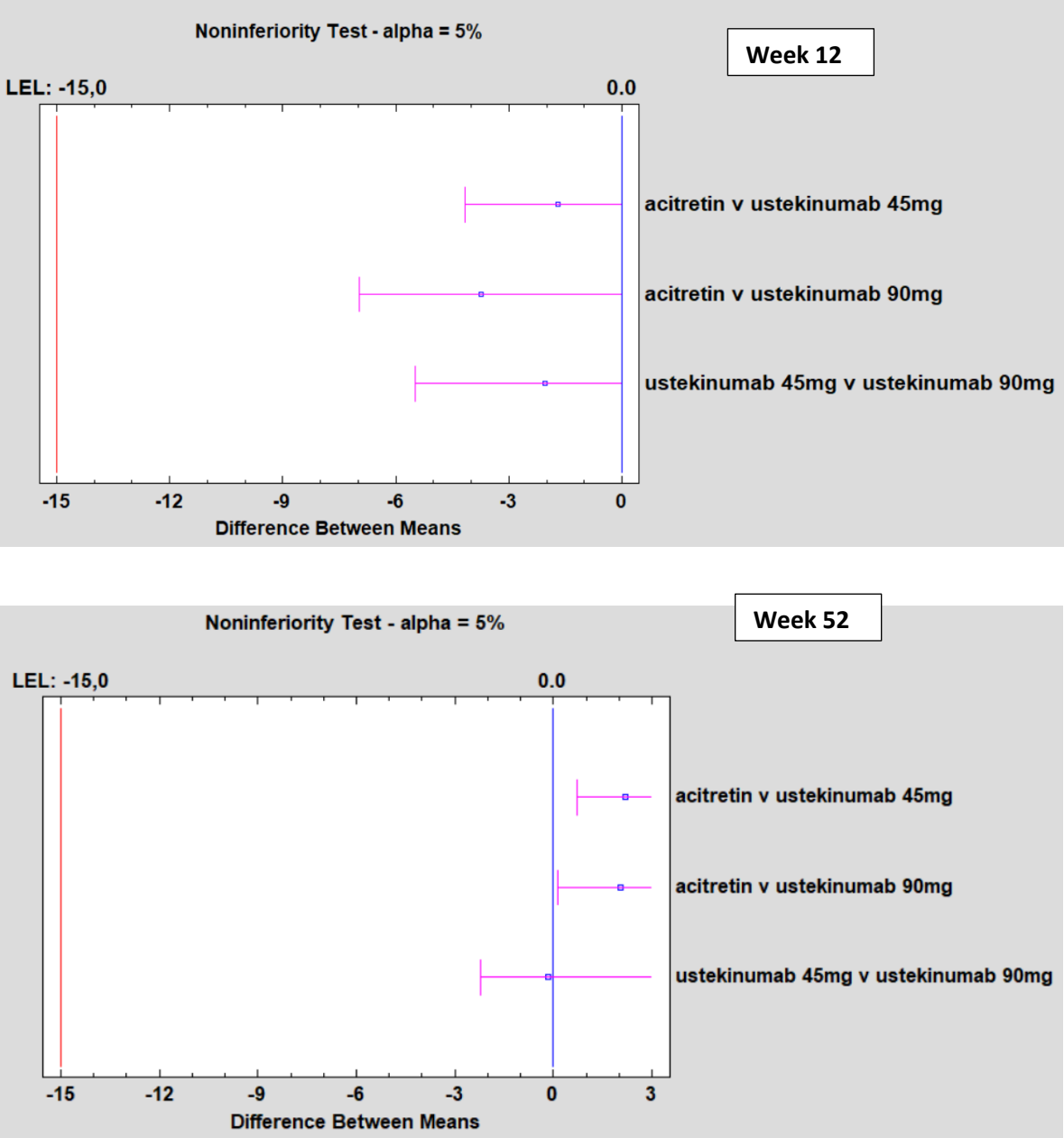

Figure 3. Non-inferiority test for Dermatology Life Quality Index (*DLQI*) scores at weeks 12 and 52.

The QALY plot indicates the impacts of three different health interventions on the psoriasis index, where the recovery of psoriasis patients (survival or index) combined with their Health-related quality of life (HRQoL) over time (Figure 4). Overall, Figure 4 demonstrated that psoriasis

patients gained QALYs by receiving treatment of acitretin and ustekinumab at the doses 45 and 90 mg in contrast to no treatment.

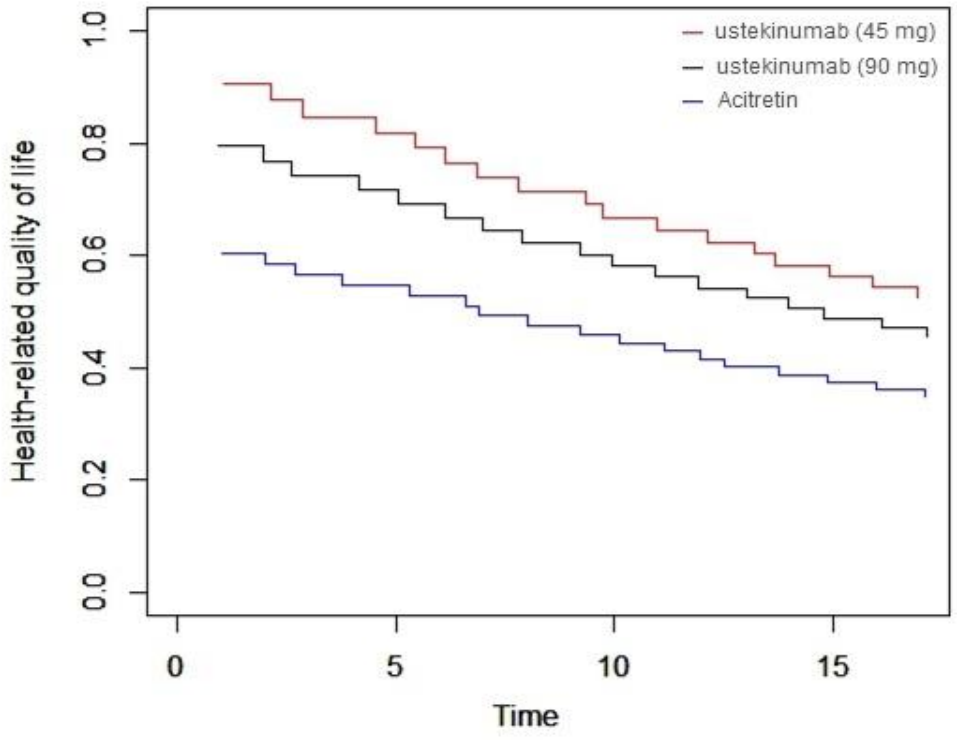

Figure 4. Survival plot showing the health-related quality of life of psoriasis patients using three different treatments: acitretin, ustekinumab (45 mg) and ustekinumab (90 mg) at the start of the treatment, after 12-weeks and 52-weeks

The area under each curve demonstrates the total QALYs gain. At the same time, in the present evaluation, psoriasis patients with different age groups who received acitretin treatment showed a lower path (HRQoL = 0.6). They reduced HRQoL sharply until they became psoriasis-free or stopped the treatment. While the psoriasis patients who received a treatment of ustekinumab 45 mg gained the highest recovery path (area under the curve) was the highest, and their HRQoL was maximum (HRQoL = 0.9) for a longer time, in addition to living with zero psoriasis index (psoriasis-free). Likewise, the patients treated with ustekinumab 90 mg also gained a higher area under the curve than acitretin treatment, indicating higher recovery paths with maximum health-related quality of life (HRQoL = 0.8), as shown in Figure 4.

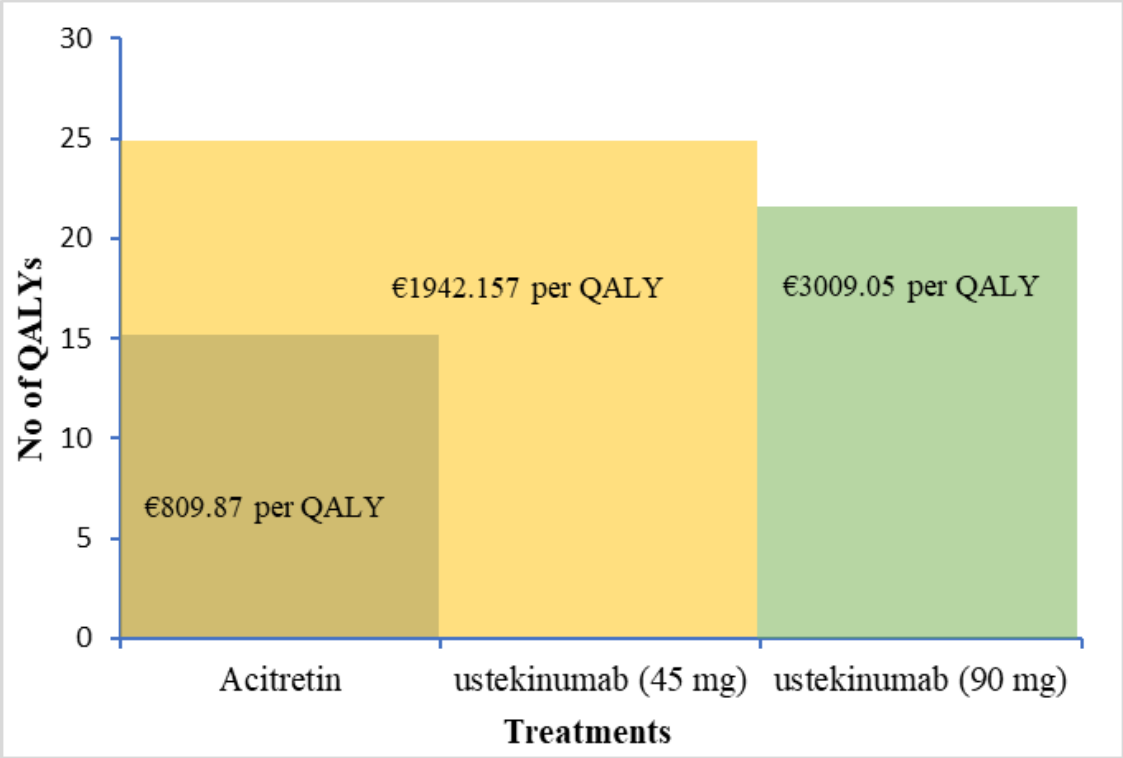

Figure 5. Number of QALYs and cost per QALY by psoriasis patients using three different treatments: Acitretin, ustekinumab (45 mg) and ustekinumab (90 mg) at the start of treatment, after 12-weeks and 52-weeks.

Overall, the maximum 24.3 QALYs have been calculated for ustekinumab (45 mg) among the psoriasis patients with a cost of €1942.15 per QALY followed by ustekinumab (90 mg), where total QALYs were 21, and the cost for per QALY was €1942.15 per QALY as shown in Figure 5. However, a total of 15 QALYs were calculated against treatment by acitretin for psoriasis pateints over time and each QALY costs for €809.87 compared to other treatments. Overall, One-Way ANOVA exhibited a substantial difference ($F\ (df) = 13.467\ (2);\ p < 0.001$) between total QALYs gained by psoriasis patients using treatment acitretin, ustekinumab (45 mg) and ustekinumab (90 mg) as shown in Figure 5. It revealed that the psoriasis index, including PASI, BSA, and DQLI, significantly ($p < 0.05$) reduced to zero after 12 and 52 weeks of treatment by ustekinumab (45 mg) than acitretin and ustekinumab (90 mg) indicated by asterisks in Figure 6.

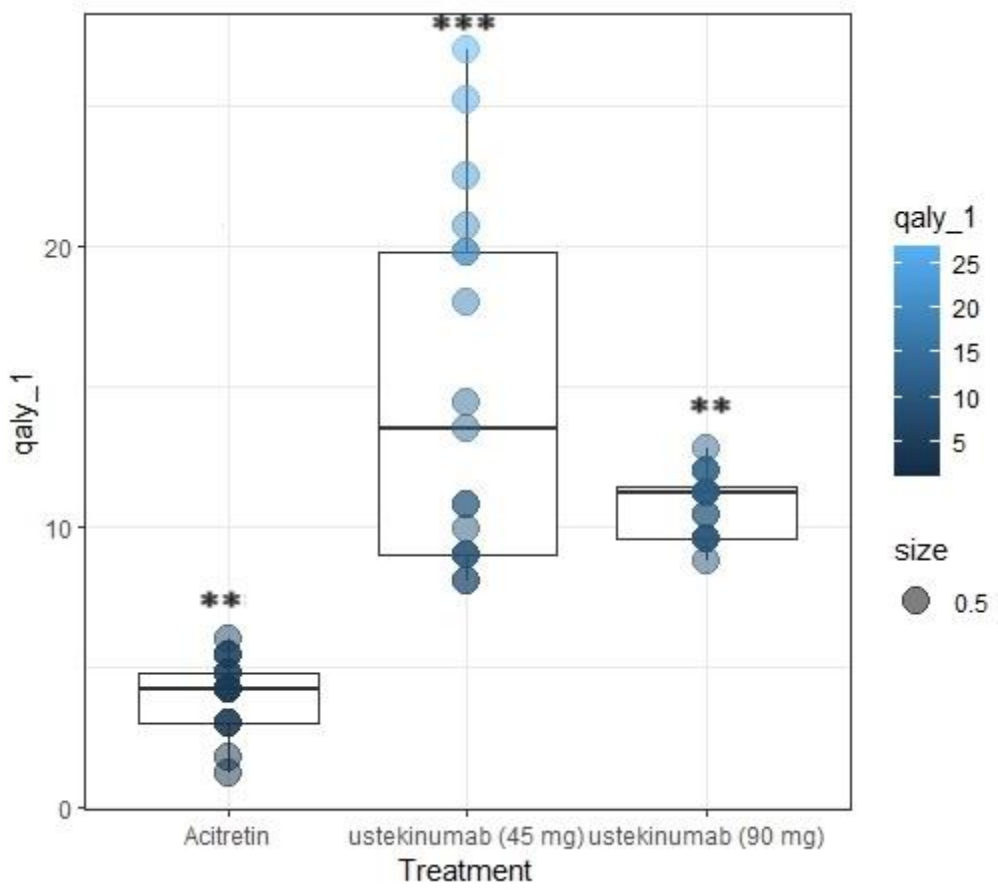

Figure 6. A box plot indicating One-Way ANOVA results that reveal the significant difference *(* = p < 0.05; ** = p < 0.001; *** = p < 0.0001*) between the QALYs gained by psoriasis patients using three different treatments of Acitretin, ustekinumab (45 mg) and ustekinumab (90 mg) at the starting of the treatment, after 12-weeks and 52-weeks.

Table 12 indicates the output of incremental and decremental cost-effective ratio for treatment acitretin, ustekinumab 45 mg, and ustekinumab 90 mg using icer function by which dominance status (D = Strong dominated; ND = non-dominance; ED = extended or week dominance) is visualized in ascending order by cost. Results showed that ustekinumab 45 mg treatment had €-1124.25, €3721.7, and €2953.6 ICER at treatment start, 12-week and 52-week duration for PASI_score respectively. It reveals that at the start of treatment, ustekinumab 45 mg treatment was not dominant (decremented) acitretin in reducing PASI_score. In contrast, after 12 and 52 weeks, ustekinumab 45 mg was more dominant than acitretin, increasing its impact in

reducing the psoriasis area severity index. Similar trends were observed by ustekinumab 90 mg in the case of PASI index as compared to acitretin, where ICER was €-872.095, €9716.6, and €3626.2 at treatment start, 12-week and 52-weeks with non-dominance and strong dominance status than acitretin respectively as shown in Table 12.

In the case of BSA, ustekinumab 45 mg status was completely dominant to extended dominant as compared to acitretin by indicating €5312.14, €3721.72, and €2953.77 incremental cost-effectiveness ratio at treatment start, 12-week and 52-week respectively. In contrast, ustekinumab 90 mg was dominated by acitretin at 12 weeks and 52 weeks in reducing body surface area index. It reveals that ustekinumab 90 mg was dominant at the time of treatment start. However, it converts dominated by acitretin after 12 and 52 weeks of treatment.

In the case of DLQI, ustekinumab 45 mg had a decremental cost-effectiveness ratio than acitretin at the start of treatment and after 12 weeks of treatment, while after 52 weeks, ustekinumab 45 mg became dominant with incremental cost-effectiveness ration €7048.3, in contrast, ustekinumab 90 mg showed ICER at start of treatment and after 12-week (€1776.689 and €4970.41), which is dominant than acitretin. However, ustekinumab 90 mg did not reduce the DLQI, as shown in Table 12.

Table 12. Incremental and decremental cost-effective ratio analysis of three different treatments (acitretin, ustekinumab (45 mg), and ustekinumab (90 mg)) on different psoriasis index including PASI, BSA and DLQI scores using three different time strategies (treatment start, 12-weeks and 52-weeks) among psoriasis patients.

Porasis_index	Treatment	Strategies	Cost	Effect	Inc_Cost	Inc_Effect	ICER/DCER	Status
PASI_index	Acitretin	Treatment_start	1762.87	11.2353	NA	NA	NA	ND
		12-weeks	1762.87	9.87059	NA	NA	NA	ND
		52-weeks	1762.87	6.95882	NA	NA	NA	ND
	ustekinumab (45 mg)	Treatment_start	19824.9	27.3	-18061	16.065	-1,124.25	ND
		12-weeks	19824.9	5.01765	-18061	4.85294	3721.7	D
		52-weeks	19824.9	0.84375	-18061	6.11507	2953.6	D
	ustekinumab (90 mg)	Treatment_start	19817.2	31.9375	-18054	-20.7022	-872.095	ND
		12-weeks	19817.2	8.0125	-18054	1.85809	9716.6	D
		52-weeks	19817.2	1.9875	-18054	4.97882	3626.2	D
BSA_index	Acitretin	Treatment_start	1762.87	8.735294	NA	NA	NA	ND
		12-weeks	1762.87	7.117647	NA	NA	NA	ND

		52-weeks	1762.87	5.323529	NA	NA	NA	ND
	ustekinumab (45 mg)	Treatment_start	19824.93	27.3	-18061.3	3.411765	5,312.14	D
		12-weeks	19824.93	1.794118	-18061.3	1.794118	3721.72	D
		52-weeks	19824.93	3.698529	-18061.3	3.698529	2953.57	ED
	ustekinumab (90 mg)	Treatment_start	19817.19	31.9375	-18054.3	-34.6397	521.2025	ND
		12-weeks	19817.19	-15.3824	-18054.3	-15.3824	1173.702	ND
		52-weeks	19817.19	2.823529	-18054.3	2.823529	-3626.22	D
DLQI_index	Acitretin	Treatment_start	1762.87	8.588235	NA	NA	NA	ND
		12-weeks	1762.87	5.117647	NA	NA	NA	ND
		52-weeks	1762.87	4	NA	NA	NA	ND
	ustekinumab (45 mg)	Treatment_start	19824.93	27.3	-18061.3	-12.4706	1448.309	ND
		12-weeks	19824.93	-1.58824	-18061.3	-1.58824	11371.91	ND
		52-weeks	19824.93	2.6	-18061.3	2.5625	-7048.3	D
		Treatment_start	19817.19	31.9375	-18054.3	-10.1618	1776.689	ND

	ustekinumab (90 mg)	12-weeks	19817.19	-3.63235	-18054.3	-3.63235	4970.415	ND
		52-weeks	19817.19	2.5	-18054.3	2.5	-7221.72	ED

NA = not applied; ND = not dominant, D = Dominant; ED = Extended/weak dominant

Negative ICER for treatment means treatment had a decremental impact on the psoriasis index compared to other treatments and was considered a decremental cost-effectiveness ratio.

This study applied cutpoint selection strategies that maximize the Net Monetary Benefit (NMB) and offer several alternatives for built-in and user-specified cutpoint selection procedures, where {predictNMB} got its start. In this study, the *"do_nmb_sim()"* function is used in the NMB run. Many datasets were created based on their NMB, which defined each square of the confusion matrix that resulted from binary classification to evaluate NMB.

TP: True Positives, accurately anticipated outcomes that result in required medical intervention

TN: True Negatives, accurately anticipated non-events that avert needless medical intervention

FP: False Positives, Inaccurately projected positive results that prompt needless medical intervention

FN: False Negatives, inaccurately anticipated non-events that prevent patients from receiving essential care

A get_nmb_sampler() function was used to create the NMB sampler function, which su pplied the simulation's data. In this study, relative to no standard cure for psoriasis, the interventi on Acitretin, ustekinumab 45 mg and ustekinumab 90 mg is linked to a hazard ratio of 0.25, 0.11 1, and 0.125 for psoriasis under intervention conditions. For effective prevention, this study empl oyed a probability-weighted cost saving, which comes out to €1762*(0.25) = €441, to €19825*(0 .125) = €2478, to €19817*(0.111) = €2119.67. This study also included a utility loss (lost QALY s) of 0.247 due to the patient developing psoriasis because we are interested in how this affects th e patient.

The model offers metrics for each medication (acitretin, ustekinumab 45, and ustekinumab 90 mg) about its effectiveness, expense, and effect on patients' quality of life. When the treatment's cost exceeds its benefits, negative numbers in the NMB columns (the first three columns) show a net monetary loss. The magnitude of the negative values shows the size of the financial loss. When the advantages of the treatment exceed the disadvantages, there is a net monetary gain, as indicated by positive numbers in the NMB columns. The size of the positive values represents the amount of the profit. The willingness to pay (WTP) values are crucial when determining whether a treatment is cost-effective, which is 50258 euros in this study. A higher NMB than the WTP criterion indicates that the treatment is cost-effective. The effect and cost of treating patients in the high-risk group are shown in the columns labelled "high-risk group treatment effect and cost (Table 13). Customizing treatments to particular patient profiles is crucial.

Table 13. Illustrating the NMB for acitretin, ustekinumab 45, and 90 mg among psoriasis patients associated with true positive s, false positives, false negatives and true negatives with QALY lost and willingness to pay (WTP) revealing the magnitude high -risk group treatment costs and effects.

Drugs	TP	FP	TN	FN	Qalys_lost	WTP	High-risk group treatment effect	High-risk group treatment cost
Acitretin	-1712.48	-1433.72	0	-432.43	0.245	50258	0.355372	1433.729
	-1586.34	-1359.083	0	-434.12	0.246	50258	0.476507	1359.083
	-1634.27	-1386.47	0	-434.45	0.246	50258	0.429635	1386.475
Ustekinumab 45 mg	-8666.57	-2463.95	0	-9083.69	0.458	50258	0.317169	2463.954
	-8646.53	-2466.71	0	-9032.78	0.455	50258	0.315844	2466.701
	-7629.26	-2471.33	0	-9053.05	0.456	50258	0.430255	2471.336
Ustekinumab 90 mg	-3507.65	-2454.34	0	-2190.46	0.111	50258	0.519139	2454.341
	-3899.43	-2508.25	0	-2632.65	0.132	50258	0.471565	2508.253
	-3798.64	-2483.69	0	-2556.55	0.129	50258	0.485657	2483.691

TP = True Positive; FP = False Positive; TN = True Negative; FN = False Negative

Table 14. Summary of NMB simulations indicating minimum, 1st quarter, median, mean, 3rd quarter, and maximum NMB values for drugs acitretin, ustekinumab 45, and ustekinumab 90 mg against psoriasis patients.

Drugs	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
acitretin	-6427	-5685	-5484	-5482	-5263	-4481
ustekinumab 45	-28086	-26983	-26575	-26571	-24753	-24753
ustekinumab 90	-24387	-23730	-23545	-23524	-23307	-22620

In Table 14 and Figure 7a, Acitretin has a range of NMB values from approximately -6427 to -4481. The negative values indicate that, in general, using acitretin results in a monetary loss. Meanwhile, Ustekinumab 45 shows a broader range, with NMB values from approximately -28086 to -24753 (Table 14 and Figure 7b). This range suggests that ustekinumab 45 mg may result in more significant monetary losses than acitretin. Ustekinumab 90 has the narrowest range, with NMB values ranging from approximately -24387 to -22620 (Table 14 and Figure 7c).

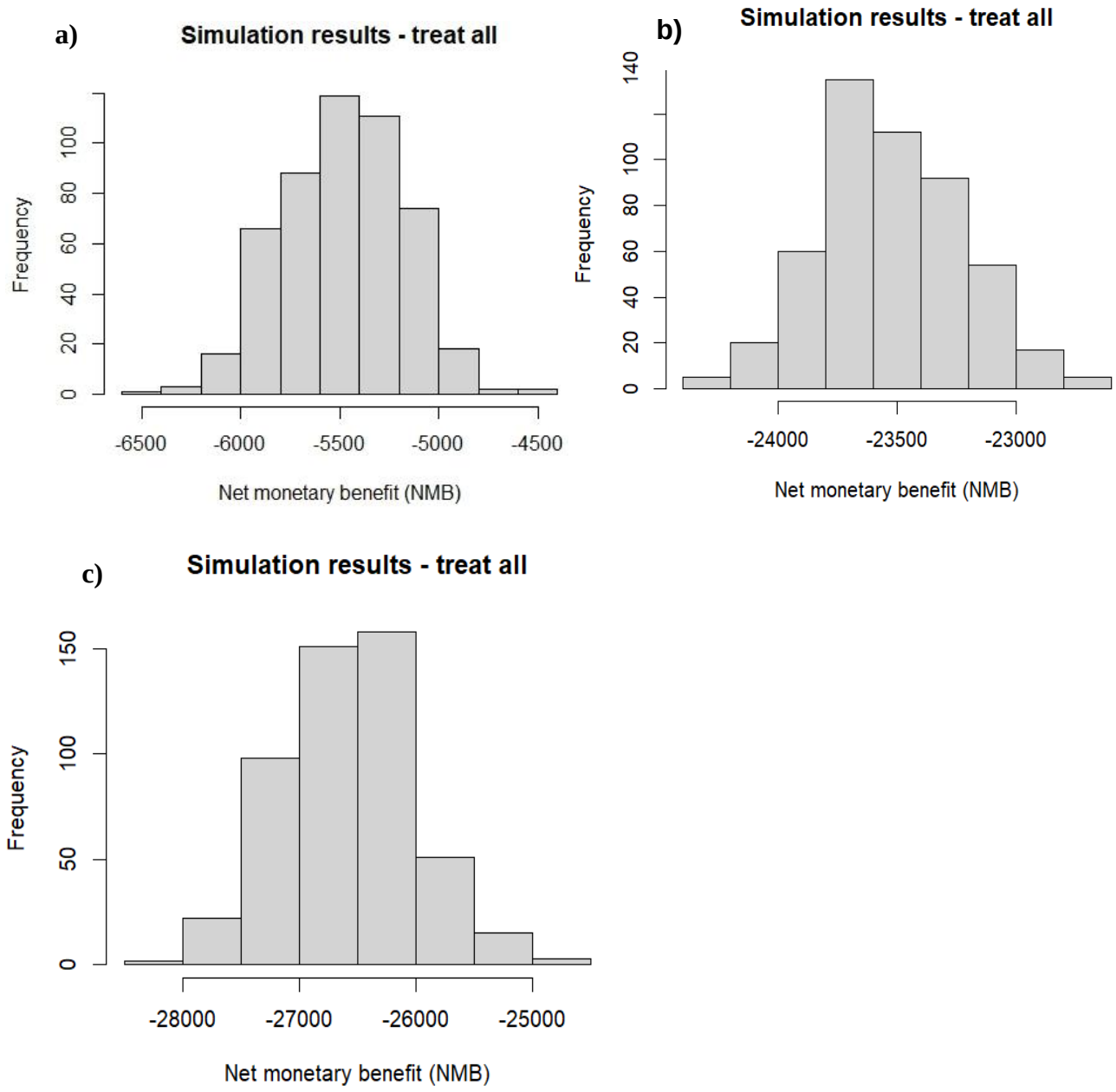

Figure 7. Histograms indicate NMB simulations indicating treatment. All simulations have NMB values for drugs acitretin, ustekinumab 45, and ustekinumab 90 mg against psoriasis patients.

Ustekinumab 90 may have a slightly more favourable financial outcome than ustekinumab 45 but is still associated with monetary losses (Table 14; Figure 7). Overall, the summary provides insights into the distribution of NMB values for each drug, allowing decision-makers to assess the financial implications of using these drugs in combination. The negative values indicate that the treatments may not be cost-effective and result in financial losses. However, the specific choice among these drugs depends on factors like efficacy, safety, and patient outcomes.

Figure 8-10 indicates the simulation thresholds for the NMB Model by using the inbuild cut point simulation methods "all", "none", "value_optimising", "youden", "cost_minimising", "prod_sens_spec", "roc01" and "index_of_union". The proportion of randomly positive patients who received a higher likelihood of an injury than randomly negative patients (and vice versa) is represented by the AUC of 0.82 for this study model. The AUC's useful characteristic is its consistency across different probability thresholds. In our instance, an AUC of 0.90 indicates that relative to patients who do not acquire psoriasis, the model will attribute an increased probability of developing one to about 90% of patients.

All index and cutpoint method simulations for the NMB Model used for all three treatments (acitretin, ustekinumab 45, and ustekinumab 90 mg) suggested net monetary loss in the treatment (Fig 9-11). Treat-all threshold indicated that the overall NMB values are negative in all simulations, indicating that the treatments (acitretin, ustekinumab 45, and ustekinumab 90 mg) are associated with a net monetary loss compared to not treating psoriasis patients. While the ‘none’ indicated that when no treatment is applied, there is a monetary cost associated with the condition, which is represented by the negative NMB values, this served as the baseline for comparison. Likewise, the ‘value_optimizing’ metric suggests that the optimal threshold for treatment varies in each simulation, and it is still associated with a net monetary loss. The threshold optimized for ‘Youden's Index also results in a net monetary loss in each simulation. Cost_minimizing threshold minimized costs still lead to a net monetary loss.

A prod_sens_spec indicated that balancing sensitivity and specificity for cost-effectiveness does not change the negative NMB values. Roc01 indicated that the threshold that maximizes Youden's Index is associated with a net monetary loss in all simulations. Likewise, balancing the index of union for sensitivity and specificity results in a net monetary loss in each simulation.

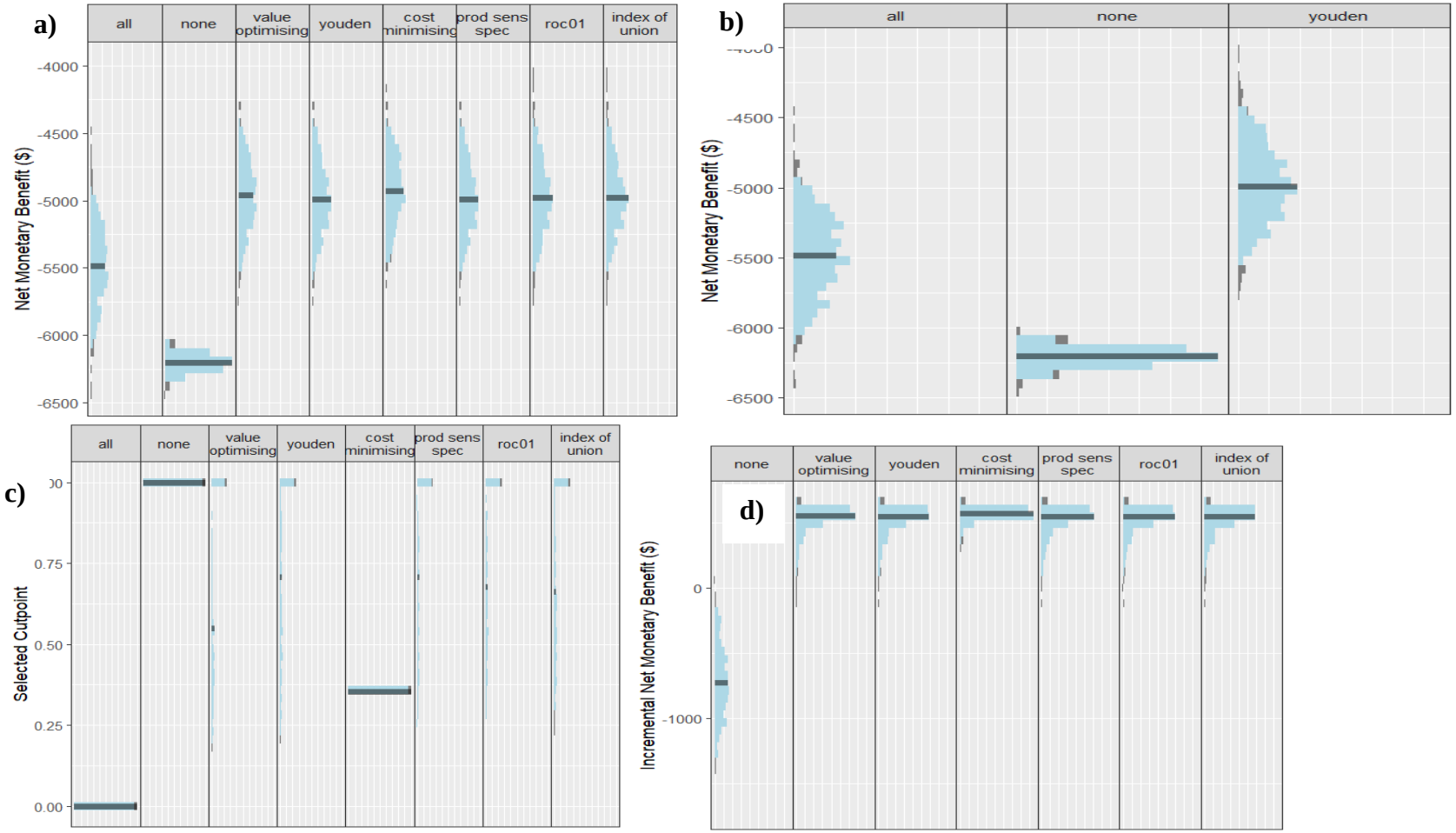

Figure 8. Primary analyses of NMB (a, b) and incremental NMB (d) associated with each cutpoint selection method (c) for acitretin, respectively.

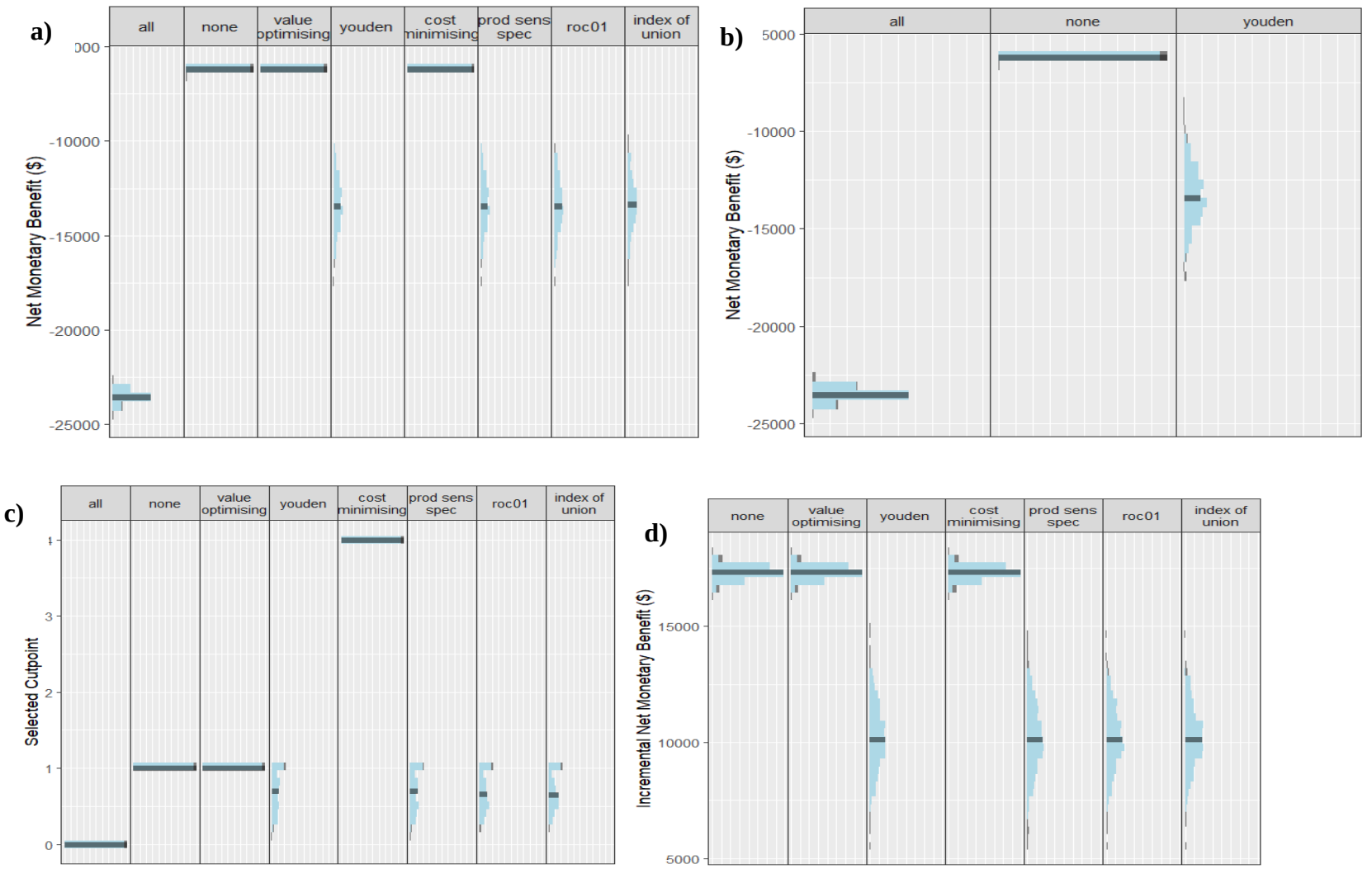

Figure 9. Primary analyses of NMB (a, b) and incremental NMB (d) associated with each cutpoint selection method (c) for ustekinumab 45 respectively.

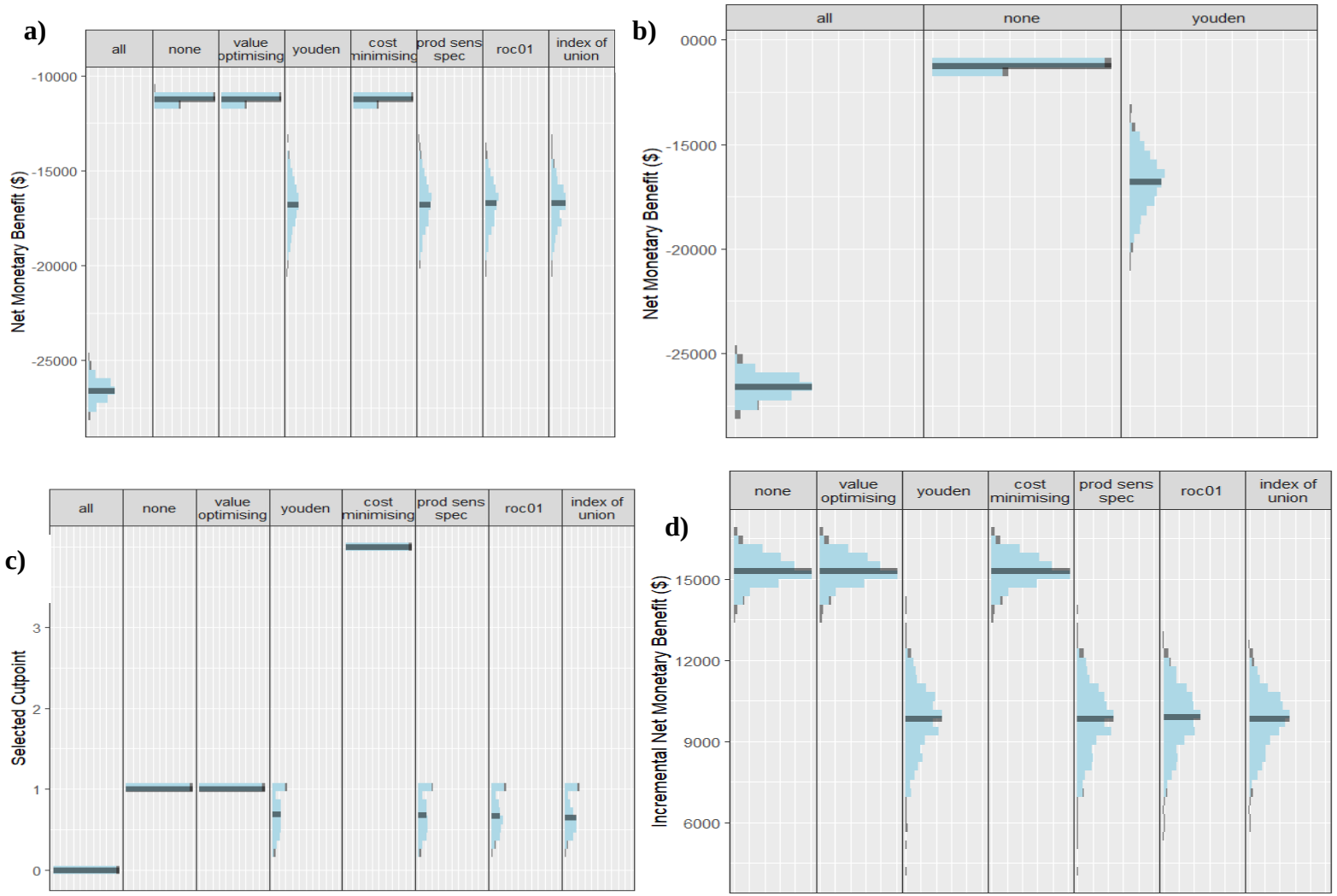

Figure 10. Primary analyses of NMB (a, b) and incremental NMB (d) associated with each cutpoint selection method (c) for ustekinumab 90, respectively.

6. DISCUSSION

In Croatia, according to the guidelines, acitretin is recommended as the first line of treatment for palmoplantar psoriasis and erythrodermic psoriasis, and in other clinical cases of vulgar psoriasis, preference is given to methotrexate due to its better effectiveness and fewer side effects (59). Ustekinumab is indicated for patients with moderate to severe psoriasis (PASI and/or BSA>15% and/or DLQI>15) who have not responded to, cannot tolerate, or have contraindications for at least two different previously applied systemic medications, including PUVA therapy, retinoids, cyclosporine, and methotrexate, as suggested by a dermatovenerologist (60).

The main aim of this study was to assess the economic implications of using acitretin versus ustekinumab (45mg and 90mg) for treating severe psoriasis. The findings revealed that treatments with acitretin and ustekinumab at 45mg and 90mg in psoriasis patients increased QALYs compared to no treatment. The findings of the non-inferiority test (Figure 3) indicated that 45 and 90mg dosages of ustekinumab are non-inferior to acitretin, staying above the set non-inferiority margin of -15.0. These findings imply that both doses of ustekinumab are at least as effective as acitretin in treating psoriasis. That is important in non-inferiority trials, which aim to prove that a new treatment is not substantially less effective than an existing one, thereby positioning ustekinumab as a viable alternative in psoriasis therapy. This finding is particularly relevant given the chronic nature of psoriasis, which often necessitates long-term treatment approach. Using ustekinumab without losing efficacy compared to acitretin provides more options in treatment planning, which is especially beneficial for patients who may not respond well to or tolerate acitretin. In particular, the study found that at both 12 and 52-week intervals, ustekinumab a 45mg and ustekinumab a 90mg proved to be clinically more efficient when compared to acitretin. In particular, it can be concluded that at both the 12 and 52-week marks, ustekinumab a 45mg and ustekinumab a 90mg proved to be clinically more efficient when compared to acitretin.

This study compared the cost of these drugs with three outcomes of PASI, BSA, and DLQI scores. In the case of the ICER for PASI, acitretin was less dominant compared to 45mg and 90mg doses of ustekinumab at 12 and 52 weeks. Similarly, for the outcome of BSA, ustekinumab a 45mg showed a clear dominance against acitretin at 52 weeks. For ustekinumab 90mg, during the 12-week and 52-week evaluations, acitretin surpassed it in reducing BSA. Lastly, in the domain of DLQI, ustekinumab at 45mg portrayed a decremental cost-effectiveness ratio compared to acitretin

at the onset and the 12-week mark. However, by the 52-week mark, this 45mg dosage manifested dominance with a noted incremental cost-effectiveness ratio. Contrarily, ustekinumab at 90mg showcased a superior ICER against acitretin at the treatment's initiation and the 12-week checkpoint, but it did not yield considerable advancements in DLQI by 52 weeks.

As in health economic research, assessing both clinical outcomes and associated costs is crucial; therefore, to discuss these findings, we have structured it into distinct sub-sections as a comparison of clinical effectiveness, cost-effectiveness, cost-utility and net monetary benefit between ustekinumab and acitretin.

6.1. Comparative Clinical Effectiveness of Ustekinumab and Acitretin

Acitretin, a second-generation systemic retinoid, was approved for managing psoriasis in 1997 (61). Likewise, ustekinumab secured approval for addressing chronic plaque psoriasis in 2013 (62). These approvals set the stage for evaluating the clinical efficacy of these drugs by utilizing distinct clinical outcomes. Multiple types of clinical outcomes can be used to assess their clinical efficacy. Among these measures, the PASI emerges as a distinguished metric, offering a quantitative evaluation of the severity of psoriatic lesions (63). As a vital instrument for objectively appraising the extent and intensity of psoriasis, the PASI has become an indispensable benchmark in clinical practice and research. This metric enables precise monitoring and tailored management strategies for individuals affected by psoriasis, quantifying the treatment's impact on patients' quality of life and determining treatment courses (63–65). In this investigation, although the PASI score decreased for all treatments, notable differences were observed between the interventions. Specifically, for acitretin, the score reduced from 11.54 to 6.01, from 27.30 to 0.79 for ustekinumab 45mg, and from 31.94 to 1.99 for the ustekinumab 90mg dosage at 52 weeks, respectively. Importantly, similar trends were observed for the other two metrics of BSA and DLQI.

While acitretin has long been a trusted treatment for psoriasis, in the past decade, biologics have brought a transformative change to the psoriasis treatment landscape (66). The studies suggest ustekinumab is an appropriate treatment choice for individuals with psoriasis (67). On the other hand, acitretin is notably effective in treating psoriasis. However, several research findings indicate that as a standalone therapy, it might be less potent than other conventional and biological agents (66,68). In a study by Noor et al., 142 patients were equally divided into two groups, each containing 71 participants. One group was treated with a 25 mg deep intramuscular methotrexate

injection weekly, while the other received a daily oral dose of acitretin at 0.4mg/kg. After 24 weeks, the effectiveness of the treatments was gauged by the reduction in their PASI scores. The results revealed that 53.5% of methotrexate groups responded excellently, achieving PASI-75%.

Conversely, in the acitretin group, only 25.3% exhibited a similar excellent response (69). Similarly, in a trial by Gisondi et al. in the 24th week, 45% of patients in the etanercept group achieved a PASI response. In the acitretin group, 30% reached this response, while in the group treated with etanercept and acitretin, 44% achieved it. Both etanercept groups showed a statistically significant difference compared to the acitretin-only group ($p = 0.001$) (3). Several other uncontrolled studies and individual case reports show that combining biological therapies with retinoids has been documented as an effective treatment for psoriasis (70).

Numerous studies have also been conducted to compare the impact of biological agents, including ustekinumab, on the PASI with conventional treatments. A systematic review and meta-analysis of randomized controlled trials were undertaken to assess the efficacy of systemic treatments for moderate-to-severe psoriasis. The primary measure of effectiveness was the proportion of participants achieving a 75% improvement in PASI scores between the 8th and 16th weeks. Among the 48 pertinent RCTs, comprising 16,696 patients, 11,178 were assigned to biologics, while 1,888 were administered conventional treatments. The conclusion was that the biologics exhibited superior efficacy to all traditional treatments, including acitretin (62). In another extensive review by Nast et al., 25 randomized clinical trials were analyzed. The evaluation of PASI for ustekinumab indicated that its pooled risk ratios were 11.39 (95% CI: 8.94-14.51), underscoring its sustained effectiveness compared to a placebo over an extended period (71).

6.2. Comparative Cost-effectiveness Ustekinumab and Acitretin

In our analysis covering 52 weeks, the 45mg dose of ustekinumab demonstrates superior cost-effectiveness when compared to both acitretin and the 90mg dose of ustekinumab. Initially, the higher cost of ustekinumab might create the perception of it being less cost-effective. Studies, such as Nast et al. had similar perception (72). However, as the study progressed, its cost-effectiveness became increasingly evident. Moreover, the prerequisite clinical tests before initiating acitretin treatment contribute to its overall expenses. These mandatory tests encompass a complete blood count (CBC), liver function tests, and a lipid profile (59). Consequently, in our investigation, the costs for ustekinumab 45mg (€2891.22) and ustekinumab 90mg (€2889.93) were lower compared to acitretin (€3924).

Various studies in the literature have come to different conclusions about the cost-effectiveness of different treatments for psoriasis, influenced by factors like the treatment duration and the comparator treatment. A study conducted in Brazil by Riveros et al. indicated that among four biological therapies, adalimumab was the most cost-efficient for moderate-to-severe psoriasis at R$120,981.45/PASI75, with ustekinumab trailing closely at R$126,336.67/PASI75 (73). Similarly, an extensive systematic review that scrutinized the cost-effectiveness of psoriasis treatments included 53 papers for its final assessment. Adalimumab was deemed cost-effective in seven articles, while ustekinumab was recognized as such in four articles. Notably, no research found acitretin a cost-effective option in the review. While among the studies reviewed, none made a comparison between ustekinumab and acitretin. Nevertheless, we identified studies that compared conventional systemic agents with biological ones (74). However, these studies were dated, limiting their findings' applicability to the current scenario (74–76).

The appearance of adverse effects can also affect the cost-effectiveness of acitretin. In our study 13 patients in the acitretin group discontinued treatment due to adverse effects or abnormal laboratory test results. Although our research did not explicitly explore the economic implications of these adverse effects, it is evident that acitretin is likely to incur higher costs compared to ustekinumab in this context. To support this position, we did not find any studies specifically addressing the impact of adverse effects on the cost-effectiveness of acitretin. However, a study by Pearce et al. focused on the cost-effectiveness of systemic treatments over 12 weeks. According to this study, acitretin cost $2729/1% of patients achieving PASI-75, ranking second in cost-

effectiveness, with methotrexate being the most cost-effective at $623/1% of patients achieving PASI-75.

Nevertheless, it was concluded that while methotrexate was the most cost-effective systemic therapy for severe psoriasis, its side effects made it a less ideal treatment option (76). Similar considerations may apply to acitretin. Although some studies supported using acitretin due to the absence of life-threatening adverse effects, it was also suggested that acitretin could be a viable choice in areas where access to biological agents is limited, which underscores the potential safety advantages of biological agents over acitretin (77,78).

6.3. Comparative Cost-Utility Analysis of Ustekinumab and Acitretin

In healthcare's cost-utility evaluations, HRQoL and QALYs play pivotal roles (79). HRQoL delves into the influence of health status on the overall quality of life, grounded in the more expansive concept of Quality of Life (QoL) (80). This concept covers health's physical, psychological, and social aspects (81). Treatments may improve quality of life but also have implications for lifespan. However, though HRQoL assessments focus on the effects of treatments on life quality, they do not consider the treatments' impact on length of life. For this purpose, QALYs provide an integrated assessment, combining lifespan and life quality into a single metric. In cost-utility analysis, QALYs assess a treatment's effectiveness by multiplying the added years of life by the expected quality of those years, effectively combining the dual benefits of treatment—life extension and quality improvement—into one comprehensive metric (82).

Our study examined the cost-utility of ustekinumab (45mg and 90mg) and acitretin for treating psoriasis, focusing on their impact on QALYs and HRQoL. This integrated approach enhances the understanding of these treatments' overall cost and utility. Overall, the HRQoL and QALY results were more favorable for ustekinumab 45mg, with an HRQoL score of 0.9. Furthermore, the highest calculated QALY for ustekinumab 45 mg was 24.3, costing €1942.15 per QALY. This study's findings align with prior research highlighting ustekinumab's effectiveness in enhancing the quality of life for psoriasis patients. However, earlier studies, while consistent with these results, either focused solely on one measurement of cost-utility or did not compare ustekinumab with acitretin (55,83,84).

In a study conducted in Columbia by Ojeda et al., the objective was to assess the long-term disease control benefits of ustekinumab in patients who were unresponsive or intolerant to other

treatments. The study employed a cost-utility analysis from the third-party payer's viewpoint, with QALYs as the outcome. Using a ten-year Markov model, it considered only direct medical costs. The model estimated QALYs based on the utility increases achieved by each treatment, with ustekinumab leading at 7.34 QALYs. The ICER showed ustekinumab as the dominant choice over alternatives (83). Similarly, a study in Thailand by authors Tangwongsiri & Leartsakulpanitch over ten years showed ustekinumab having the lowest mean annual cost at 507,502 baht, compared to etanercept (582,881 baht) and infliximab (585,462 baht). When evaluating the cost-utility ratio, ustekinumab held a 72.60% probability of being cost-effective at a threshold of 120,000 baht/QALY, significantly higher than the 13.60% probability for both etanercept and infliximab (84).

One aspect that cannot be ignored is that while ustekinumab 45 mg treatments are more expensive per QALY, the cost is counterbalanced by their substantial benefits in terms of life quality and symptom relief. Similarly, despite being less costly, acitretin offered lower HRQoL and fewer total QALYs. Although more economically feasible, it falls short of providing the same benefit as ustekinumab. However, this raises important considerations for healthcare systems where budget constraints exist. Therefore, adopting more expensive treatments like ustekinumab depends on the willingness to pay for higher QALY gains. Similarly, ustekinumab, despite its higher cost, could be recommended for patients where quality of life is a primary concern. Policymakers and healthcare providers must weigh the higher costs against the potential for significantly improved patient outcomes.

6.4. Net Monetary Benefits Analysis

Net monetary benefit (NMB) serves as a concise measure expressing the value of an intervention in monetary terms, given a known willingness-to-pay (WTP) threshold for a unit of benefit (56). In our case, the analysis of NMB for three treatments—Acitretin, Ustekinumab 45 mg, and Ustekinumab 90 mg—indicated a consistent trend toward financial losses across all options. Specifically, Acitretin exhibited the least financial disadvantage, with NMB values ranging from -€6,427 to -€4,481. In contrast, Ustekinumab 45 mg showed more substantial losses, ranging from -€28,086 to -€24,753. Meanwhile, Ustekinumab 90 mg demonstrated slightly less financial loss than its 45 mg counterpart, with NMB values between -€24,387 and -€22,620. These outcomes imply that, when solely considering the monetary perspective, none of these treatments emerges as the most cost-effective for managing psoriasis. The study employed a WTP threshold of €50,258, revealing NMB values significantly lower than this threshold for all three treatments, confirming their limited cost-effectiveness under the study conditions.

It is crucial to contextualize these NMB findings within the study's limitations. The emphasis on NMB primarily captures the financial dimension, potentially overlooking the holistic benefits of treatments, including patient satisfaction, symptom relief, and enhanced long-term health outcomes (56,85), which underscore the need to balance financial considerations with patient clinical outcomes. Similarly, the primary driver of the observed financial losses with ustekinumab was the high treatment costs. Due to this, acitretin emerged with the most minor financial disadvantage, suggesting relative cost-effectiveness. However, when considering clinical effectiveness, this conclusion may not hold.

Similarly, while biological agents are expensive globally, varying results can be expected with reduced costs in the future (86,87). Additionally, study conditions, encompassing population characteristics, study duration, and the specific economic model used, can influence results. Similarly, the chosen WTP threshold of €50,258 is a variable that can differ between countries, impacting results (88). Adjusting this threshold could alter the assessment of cost-effectiveness.

Due to these factors, making direct comparisons between our findings and previous studies is not viable due to methodological variations. Furthermore, our investigation has underscored a gap in the existing literature, revealing a lack of specific studies comparing ustekinumab with any conventional agent in NMB. However, diverse outcomes have been observed when considering studies comparing biological agents in other diseases (89). For instance, Aliyev et al. evaluated

the cost-effectiveness of ustekinumab, infliximab, or adalimumab for treating moderate-severe Crohn's disease in patients who had not responded to conventional therapy. To assess the relative value of these treatments, expressed in terms of their order of cost-effectiveness, NMB was calculated based on a willingness-to-pay threshold of $150,000 per quality-adjusted life-year in the base case. In this context, infliximab demonstrated superior cost-effectiveness compared to adalimumab and ustekinumab, with NMB of $9,943 and $29,798, respectively, in the base case. Adalimumab, on the other hand, dominated ustekinumab with an NMB of $19,855. Although all biologics yielded similar quality-adjusted life-years (approximately 3.5), their costs varied significantly, with infliximab costing $50,510, adalimumab $54,985, and ustekinumab $72,921 (90).

6.5. Policy and Healthcare System Implications

Health economic studies have emerged as an indispensable tool in shaping healthcare policy and practice, especially in an era characterized by escalating healthcare costs and finite resources (52). These studies offer a systematic approach to evaluating the cost-effectiveness of medical interventions, enabling policymakers and practitioners to make informed choices that maximize both clinical and economic outcomes (53). Moreover, in a global healthcare landscape where patients' quality of life has gained prominence, these studies provide insights into the intangible costs, ensuring a more holistic approach to healthcare decision-making (53). In essence, health economic studies are the compass that guides stakeholders in delivering optimal patient care while ensuring fiscal responsibility, a balance crucial for any healthcare system's sustainability (91).

The pathology of psoriasis poses not only physical and psychological challenges but also leads to significant economic burdens on both individual and societal levels (41). Due to this reason, a thorough understanding of the cost-effectiveness of various psoriasis treatments is imperative to ensure the best health outcomes while efficiently using limited healthcare budgets (92). Analyzing the economic impacts of psoriasis treatments provides insights that can guide decision-makers in optimizing healthcare resource allocation ensuring access to effective treatments (71).

In our case, there is a possible inclination towards ustekinumab at 45mg, given its dual benefits in terms of efficacy and economic outcomes. While the findings from our study hold substantial implications for healthcare policymakers and other pivotal stakeholders, it is crucial to interpret

them with caution due to our limited sample size. Such a constraint potentially hampers our capacity to offer robust guidance to decision-makers. Therefore, more expanded studies with larger cohorts are requisite to cement these findings and offer unequivocal guidance to policymakers. We can only provide a firm conclusion for sustainable and comprehensive treatment strategies catering to the patient's well-being and the healthcare system's financial sustainability.

6.6. Potential Limitations

While offering valuable insights, our study has constraints that should be considered when interpreting the results.

One primary limitation is the sample size. The study encompassed a relatively modest cohort, which inherently restricts the breadth and depth of our conclusions. Such a small sample size might not be entirely representative, thereby hindering the generalisation of our findings to the broader population of psoriasis patients. This challenge was amplified by excluding 13 patients from our initial pool, which further contracted our sample. However, despite these sample size challenges, we remain optimistic about the contribution of our research. We envision our study as a preliminary exploration or a pilot study, providing initial insights and setting the stage for more extensive, in-depth research in the future.

Another significant limitation pertains to the categorization of psoriasis. Our research did not segregate results based on the specific types of psoriasis, a distinction highlighted as crucial in recent literature (92). As various psoriasis types might respond differently to treatments, a stratified analysis comparing the health-economic benefits of these drugs for distinct psoriasis categories would potentially offer more nuanced and actionable outcomes.

7. CONCLUSION

While in high-income countries, one conventional therapy must show no response for prescribing biological treatment, in Croatia, two treatments must show no response. This study shows that ustekinumab in both dosages (45 mg and 90 mg) is more effective than acitretin.

Psoriasis Area and Severity Index, Body surface area, and Dermatology Life Quality Index after 12 and 52 weeks were reduced much faster in patients using ustekinumab.

Also, the non-inferiority test shows that ustekinumab (both dosages) is not inferior to acitretin as a therapy for severe psoriasis.

Regarding quality-adjusted life years, ustekinumab had a maximum reach of 24,3 QALY and 21 QALY with a price of 1942,15 euro per QALY for dosages 45mg and 90 mg, respectively. There was a statistically significant difference between treatments regarding quality-adjusted life years since acitretin had a maximum reach of 15 QALY but with a price of 809,87 euros per QALY.

The incremental cost-effectiveness ratio in this study shows the domination of ustekinumab over acitretin in reducing PASI, BSA and DLQI scores after 12 weeks of treatment. After 52 weeks for PASI and BSA, acitretin shows domination regarding DLQI after 52 weeks.

While ustekinumab enhances quality of life and clinical results more than acitretin, its high price represents a significant economic burden. Given the constraints of healthcare resources, this study emphasizes the need to weigh economic efficiency when selecting an appropriate treatment for psoriasis.

8. SAŽETAK

Psorijaza je kronična, rekurentna, autoimuna bolest kože. Procjenjuje se da u Hrvatskoj oko 80 000 ljudi ima neki oblik psorijaze, a 20% pacijenata ima srednje tešku ili tešku psorijazu. Ukupni troškovi zdravstvene zaštite oboljelih od psorijaze u svijetu procjenjuju se na 11,25 milijardi dolara godišnje.

Ciljevi ove studije bili su pokazati da primjena ustekinumaba nije inferiorna u usporedbi s acitretinom te procijeniti izravne troškove liječenja srednje teške i teške psorijaze ustekinumabom u usporedbi s acitretinom.

Provedena je retrospektivna studija koja uključuje podatke 25 pacijenata koji su primjenjivali ustekinumab i 43 pacijenata koji su primjenjivali acitretin. Podaci su prikupljeni analizom medicinske dokumentacije pacijenata.

Ukupni rezultati za HRQoL i QALY bili su povoljniji za ustekinumab 45 mg, s rezultatom HRQoL od 0,9. Najviši izračunati QALY za ustekinumab 45 mg bio je 24,3, s cijenom od 1942,15 € po QALY-u. Ustekinumab 45 mg pokazao se povoljnijim u smislu ICER-a od -1124,25 €, 3721,7 € i 2953,6 € za PASI na početku, nakon 12 tjedana odnosno nakon 52 tjedna liječenja.

Ovo istraživanje pruža uvid u složene farmakoekonomske aspekte liječenja srednje teške i teške psorijaze, ističući važnost cjelovitog pristupa procjeni troškova i uporabi različitih terapijskih pristupa.

9. ABSTRACT

Title: The pharmacoeconomic aspect of moderate and severe psoriasis treatment with biological therapy versus conventional therapy

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Zagreb, 2024

Psoriasis is a chronic, recurrent, autoimmune skin disease. In Croatia, around 80,000 people have some form of psoriasis, and 20% have moderate or severe psoriasis. The total costs of psoriasis for patients worldwide are $11.25 billion annually.

This study aimed to show that using ustekinumab shows non-inferiority compared to acitretin and to evaluate the direct cost of treatment of moderate and severe psoriasis with different treatments.

A Retrospective study included data from 25 patients using ustekinumab and 43 patients using acitretin. Data was collected by analyzing patients' medical records.

Overall results for HRQoL and QALY were more favourable for ustekinumab 45 mg, with an HRQoL score of 0.9. The highest calculated QALY for ustekinumab 45 mg was 24.3, costing €1942.15 per QALY. Ustekinumab 45 mg showed more favourable results in terms of ICER of €-1124.25, €3721.7, and €2953.6 for PASI scores at baseline, after 12 weeks, and after 52 weeks of treatment, respectively.

This research provides insight into the complex pharmacoeconomic aspects of treating moderate and severe psoriasis, highlighting the importance of a comprehensive approach to evaluating the costs and benefits of different therapeutic approaches.

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11. BIOGRAPHY

Ante Orbanić, MPharm, was born in 1990 and graduated from the University of Zagreb Faculty of Pharmacy and Biochemistry in 2014. During his studies, he was awarded the Dean's Award for scientific work on "Application of biopolymers in innovative cryopreservation procedures of animal corneas". Since 2014, he has worked as a pharmacist at City Pharmacy Zagreb.

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His primary interest is public health and pharmacoeconomics, specifically how pharmacoeconomic models can optimize healthcare outcomes and resource allocation in public health systems.