General introduction and aims of this thesis.

GENERAL INTRODUCTION

This introduction will start with a general description of psoriasis, the main disease addressed in this thesis. This will be followed by a description of two related immune-mediated inflammatory diseases namely, psoriatic arthritis, which can co-exist in patients with psoriasis, and rheumatoid arthritis, a well-established systemic inflammatory disease. The third paragraph explains two liver diseases; non-alcoholic fatty liver disease and liver fibrosis. In this thesis both liver conditions will be further investigated in their connection with psoriasis. The fourth paragraph describes comorbidities in general and in the second part of this paragraph zooms in on liver specific comorbidities. This is followed by an elaboration on how the liver is currently monitored in immune-mediated inflammatory disease. Finally we describe the aims of this thesis.

PSORIASIS

Epidemiology

Psoriasis is a serious common inflammatory skin disorder, which affects between the 0.6% and 4.8% of the population worldwide.[1] In the Netherlands the prevalence is around the 2%, which represent ±340.000 persons with psoriasis.[2] Psoriasis can start at any age, but there are two incidence peaks, one between the age of 15 to 30 and the other peak is between the age of 50 to 60.[1] Males and females are equally affect, however there are reports that psoriasis is more severe in men.[1]

Clinical

Psoriasis can be divided into different phenotypes which can co-occur within one patient. Plaque psoriasis is the most common form and is seen in 90% of the cases. This subtype is characterized by red indurated lesions which can affect any skin site; however usually extensor surfaces of the forearms and shins, peri-umbilical, perianal, and retro-auricular regions and the scalp are affected. (Figure 1) Scalp psoriasis is present in 75%-90% [3] of patients and nail psoriasis has a life time incidence of 80-90%.[4,5] Another form is pustular psoriasis; this can be generalized on the whole body or be restricted to the palms and soles, so called palmoplantar pustulosis. The generalized pustular psoriasis is characterized by white coalescing pustules on dark erythematous patches and can confluence to large lakes of pus. This can progress rapidly and be potentially life threatening. Furthermore guttate psoriasis (droplet), intertriginous or flexural psoriasis and the most severe and rare form is erythrodermic psoriasis, which can have serious complications. To classify the severity of psoriasis mostly the Psoriasis Area Severity Index (PASI) score or the psoriasis global assessment (PGA) are used.[6,7]

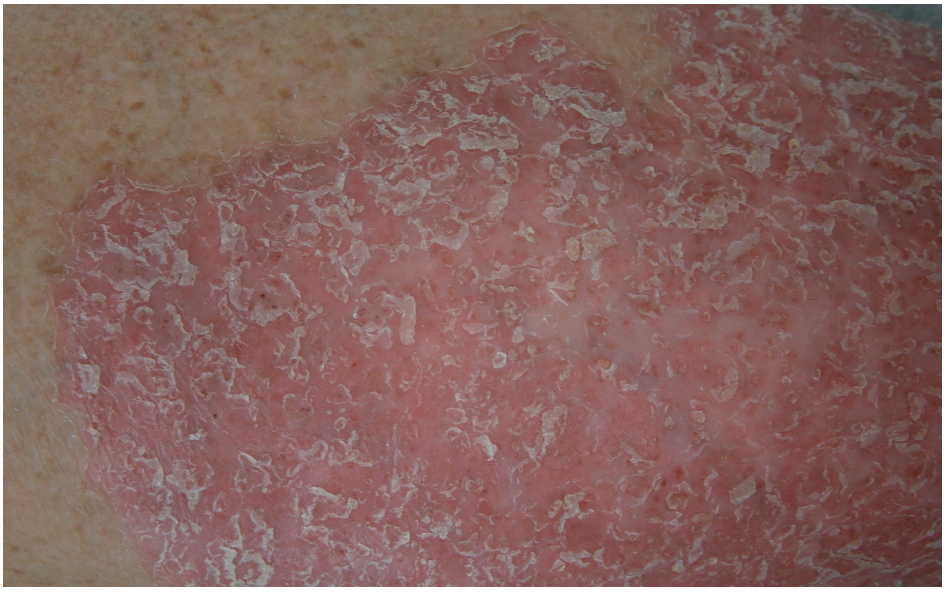

Figure 1. Clinical presentation of psoriasis

Pathology

Histopathological features of psoriasis are epidermal acanthosis, hyperkeratosis, parakeratosis and elongation of the rete ridges caused by the premature keratinocyte maturation. These features are clinically visible as thick red scaly plaques. The granular layer is minimal in size or even absent, blood vessels reaching into the tips of the dermal papillae and a mixed inflammatory infiltrate with neutrophilic granulocytes within the epidermis something leading to Munro's microabscesses. With immunohistochemical staining of CD3 an increased amount of T-lymphocytes can be demonstrated in the dermis and epidermis.[5] These activated T-cells, dendritic cells and cytokines stimulate the differentiation of T cells to Th1 and Th17 cells. The interplay of these adaptive T cells (adaptive immune system) and macrophages, mast cells and granulocytes (innate immune system) produce several mediators that induce and maintain these psoriatic hallmark features in both dermis and epidermis. (Figure 2)

Etiology

The current concept is that psoriasis is a multifactorial disease in which genetic, (neuro)immunological and environmental factors interact and cause a vicious cycle of inflammation that is insufficiently controlled by regulatory systems. In this inflammatory disease there is a complex pathogenic interaction between the innate and adaptive immune system.

The risk of getting psoriasis is higher when one or two parents are affected, respectively 28% and 65% and the lifetime disease concordance in monozygotic twin is higher with 35-73% compared to 12-20% in dizygotic twins. [9,10] These findings illustrate

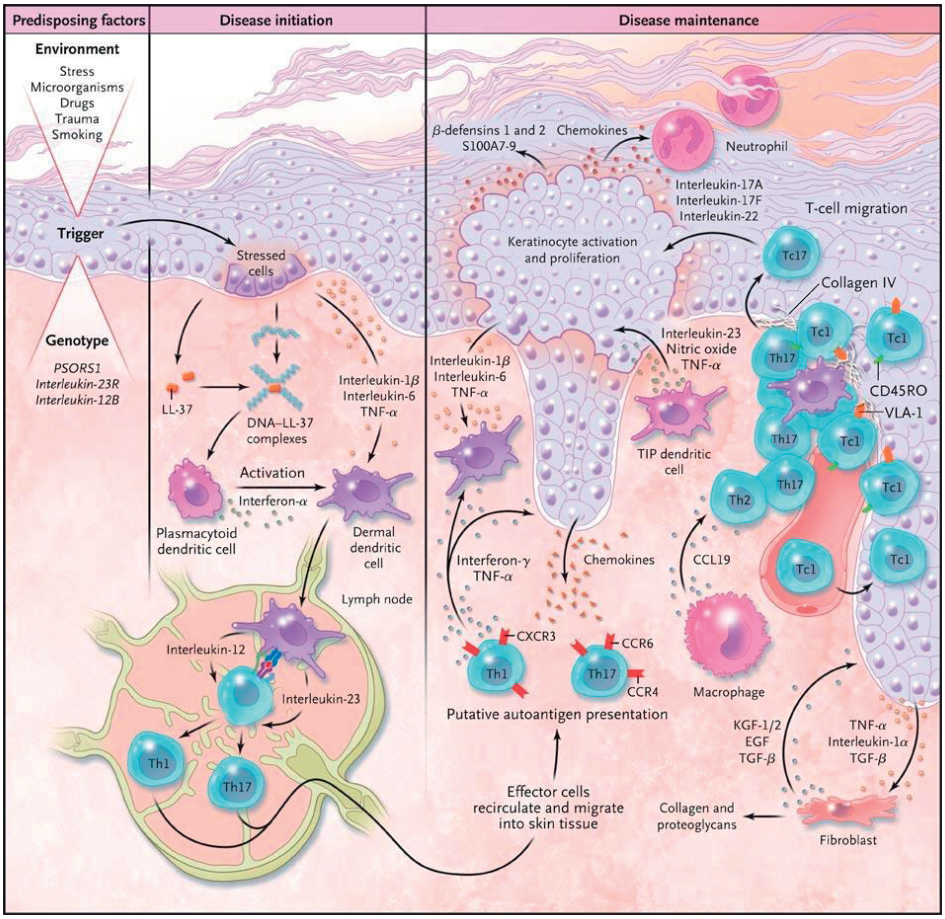

Figure 2. Schema of the evolution of a psoriatic lesion from initiation to maintenance disease. Reproduced with permission from Nestle et al [8], Copyright Massachusetts Medical Society.

a genetic predisposition in psoriasis. Genome-wide association studies (GWAS) in European-origin have identified loci in 66 genomic regions that are associated with psoriasis at genome-wide significance.[11] Of these around 18% is also related to psoriatic arthritis and 14% to single cutaneous disease.[12] Most of these genetic loci and genes are involved in the interleukin IL-23/Th17 axis of the psoriasis immunopathogenesis.[13] The cytokines of importance in this axis are IL-17A, IL-17F, IL-22, IL-26, TNF-alfa and of the TH-1 axis; TNF-alfa, IFN-gamma and IL1 and IL2, furthermore IL-23, IL-20 and IL-15 are increased in serum and lesional skin.[14] The PSOR1 locus on the HLA-Cw6 allele is related to the greatest risk factor of early onset psoriasis.[15]

Environmental factors; including medicines can trigger psoriasis and can be a reason for exacerbation or therapy resistant forms. The most well-known drugs are β blockers, ACE-inhibitors, lithium, antimalarials, and non-steroidal anti-inflammatory agents.[16] Tu-

mor necrosis inhibitors, which is an effective therapy for psoriasis can paradoxically also cause psoriasis pustulosis.[17] Other triggers are mild trauma (Koebner phenomenon), sunburn, or chemical irritants, infections e.g. streptococcal infections or HIV infection, alcohol, obesity, smoking and stress.[18-21]

Burden

Psoriasis has a high physical and psychological burden. The psychological burden measured in quality of life is even higher in psoriasis compared to congestive heart failure, myocardial infarction and cancer.[22] This may be explained by the visible disfiguration on the skin that can trigger negative reactions and low self-image as well as the itching and burning and sometimes painful sensation of the psoriasis plaques. The physical burden can even be further increased by co-existing diseases like psoriatic arthritis and a higher incidence of metabolic syndrome and several other comorbid disease e.g. depression and Crohn's disease.[8] The economic consequences are significant, high costs conducted to visits to the outpatient clinic, drugs, especially biological therapy, missed working days or even unemployed because of their psoriasis. This all together made that the WHO in 2013 recommended a raised awareness of psoriasis as a major global health problem.[5]

Therapy

Approximately three quarter of patients have mild psoriasis and are treated only with topical therapies.[23] Topical corticosteroids, vitamin D analogues, and emollients are the most applied topical treatments. Tacrolimus is mainly used for intertriginous areas and the face, while dithranol and coal tar ointment are mostly prescribed in a day care setting. Around 25% of the psoriasis patients has a moderate to severe disease severity that requires more than topical treatment. The next step is often phototherapy; narrow-band UVB and sometimes PUVA. When topical and phototherapy fail, or are contraindicated, systemic therapy is the next step. The following classic systemic agents are available: fumaric acid (induces IL-4 producing Th2 cells and generates type II dendritic cells to produce IL-10 instead of IL12/IL23), cyclosporine (calcineurin inhibitor, deceases T-cell proliferation), methotrexate (MTX) (folic acid antagonist, reduces cell proliferation) (we will discuss this later on in the introduction in more detail), acitretin (vitamin A derivate). Biological therapy is a second line therapy when conventional systemic therapies (UVB or PUVA and minimal MTX) were not tolerated, have failed or are contra-indicated. Biological therapy, monoclonal antibodies and fusion protein-based selective targeting of key mediators of inflammation, have been added to the therapeutic options the last decade and more innovative therapies are expected in the near future. The biologicals which are currently available on the market are infliximab (anti-TNF-α, soluble and transmembrane), etanercept (anti-TNF-α receptor fusion protein), adalimumab (anti-TNF-α) , ustekinumab (anti IL-12/IL-23), secukinumab (anti-IL-17A).[24]

Ixekizumab (anti -L17) is the most recently approved biological. Also recently, a new oral immunomodulative therapy, called apremilast (phosphodiesterase 4 inhibitor) was approved in Europe and USA.

RELATED IMMUNE-MEDIATED INFLAMMATORY DISEASES

Psoriasis, Psoriatic arthritis (PsA) and rheumatoid arthritis are immune-mediated inflammatory diseases (IMID).

Psoriatic arthritis

PsA is an seronegative, chronic, inflammatory joint disease, characterized by joint damage, psoriatic skin lesions, and disability.[25] The prevalence in the general population is around 0.2%.[26] Among psoriasis patients, 4.6% suffers from psoriatic arthritis visiting only a general practitioner up to around 30% in secondary dermatologic care, and this risk increases with psoriasis severity.[27,28] Patients have complaints of pain, swelling and tenderness of the joints, which reduces daily functioning and the quality of life.[29] From 15,5% up to 90% of the psoriatic arthritis patients suffer from nails involvement.[28,30] Psoriatic arthritis is also associated with cardiovascular risk factors, like obesity, hypertension, diabetes and dyslipidemia, which contributes to an increased risk of cardiovascular events and mortality.[31] In psoriatic arthritis there is a large genetic contribution with genes overlapping with psoriasis susceptibility, particularly HLA-Cw*0602, IL23R and IL-12B.[32] Activated T-cells and macrophages playing an important role in the induction of inflammatory and destructive processes in the joints.[33] Increased levels of pro-inflammatory cytokines like IL-1β, IL-2, IFN-γ and TNF-α, are found in the synovium.[33] And also the IL23/TH17 axis has been implicated in psoriatic arthritis. (Figure 3)

Rheumatoid arthritis

is a chronic seropositive autoimmune arthritis, which is characterized by synovial inflammation and destruction of the joints resulting in disability and decreased quality of life.[29,34] The prevalence varies from 0.37% to 1.0% and increases in developing countries, female gender and higher age.[34] Genetic factors are of importance in susceptibility to rheumatoid arthritis, with heritability to 60%, with a HLA locus of 30% of the overall genetic risk. [34] Also in rheumatoid arthritis there is a complex interplay between the innate and adaptive immune system. (Figure 3) Inflammatory infiltrates are found in the synovium and synovial fluid. Dendritic cells, mast cells, macrophages, neutrophils and T and B-cell producing antibodies and immune complexes playing roles in the development of the different factors of rheumatoid arthritis.[35]

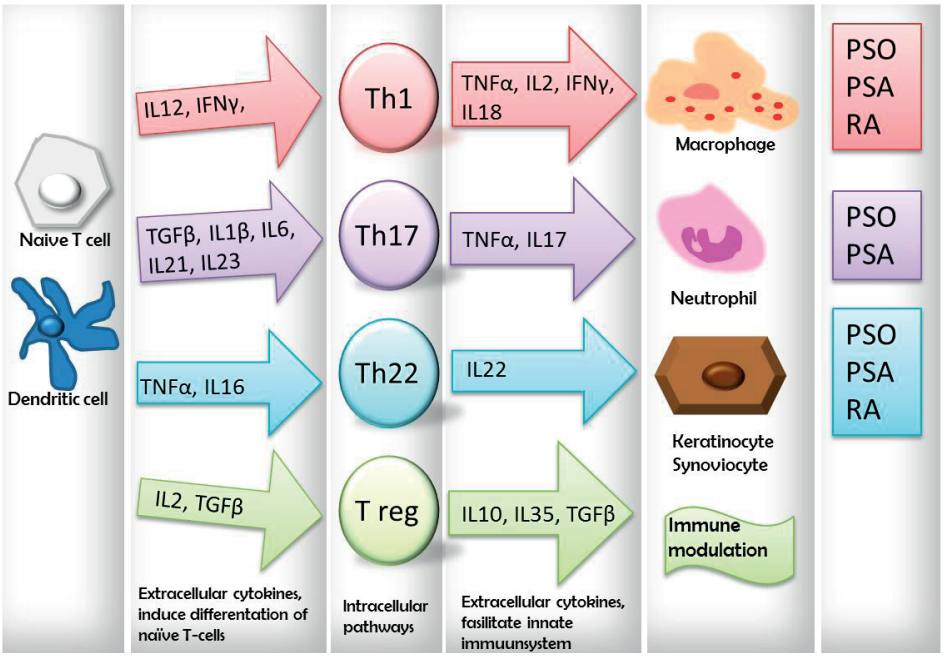

Figure 3. Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same?
The cells and cytokines involved in the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis. Abbreviations; IL, interleukin; PsA, psoriatic arthritis; Pso, psoriasis; RA, rheumatoid arthritis; TGF, tumor growth factor; Th, T-helpercells; TNF, tumor necrosis factor.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND LIVER FIBROSIS

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of liver damage, from simple fatty liver to steatohepatitis, liver fibrosis and cirrhosis and is mostly asymptomatic until cirrhosis as a final end point (Figure 4). The severity of fibrosis, the precursor of cirrhosis, predicts the occurrence of complications such as portal hypertension, hepatocellular carcinoma, liver-related morbidity and even mortality. NAFLD is divided into that with primary and that with secondary causes. Primary NAFLD is strongly related with metabolic syndrome and can only be diagnosed if causes of secondary NAFLD and excessive alcohol consumption have been excluded. Secondary NAFLD can be caused by a variety of pharmacological agents (e.g. MTX), medical or surgical conditions. The process of a simple fatty liver progressing to cirrhosis with its related complications, has a wide range that runs from two years to many decades with a mean duration of 26 years.[36] Approximately 30-40% of the people with fatty liver disease will develop non-alcoholic steatohepatitis (NASH) and almost half of these patients will progress to hepatic fibrosis.[37] Well known risk factors for this progression of hepatic fat accumulation and hepatic fibrosis are age over 50 years, obesity, insulin resistance, type

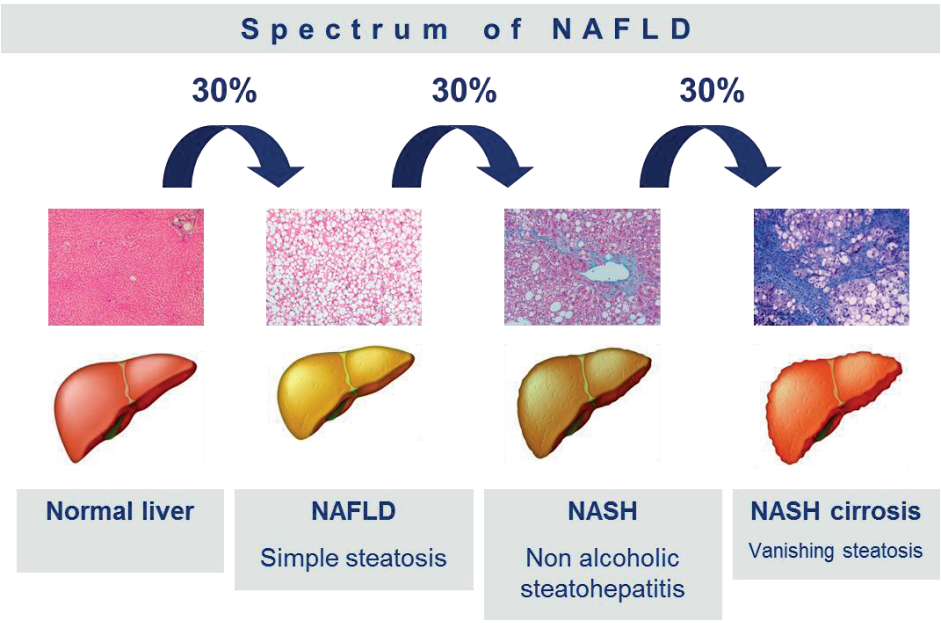

Figure 4. Spectrum of NAFLD
NAFLD refers to a wide spectrum of liver damage, ranging from mild steatosis to nonalcoholic steatohepatitis, advanced fibrosis and finally cirrhosis.

2 diabetes mellitus, increased ferritin levels and the patatin-like phospholipase domain-containing 3 (PNPLA3) I148M polymorphism, however their specific contributions and the pathological mechanisms are still not well-understood.[38-40]

In developing countries the prevalence of NAFLD is estimated around 30% in the general population and can be as high as 74% in obese patients. It is the most prevalent liver disease and it is expected that in 2020 it will be the main indication for liver transplantation.[41] Men are more affected that women and NAFLD has a peak incidence in the sixth decade of life.[42] The diagnose of NAFLD can be made on radiological imaging techniques (e.g. ultrasound or magnetic resonance technique)[43] or fatty liver index.[44] Besides liver related morbidity and mortality, NAFLD is seen more and more as a multisystem disease, with an increased risk of type 2 diabetes mellitus, cardiovascular disease and chronic kidney disease.[45] The majority of the death is attributed to the extra-hepatic comorbidities.

COMORBIDITIES

Systemic Inflammation

In many immune-mediated inflammatory diseases (IMIDs) as well as in cardiovascular disease, higher values of cytokines are found not only in the primary affected organ, but also in the serum of these patients. A frequently mentioned hypothesis is nowadays that this systemic inflammation causes the development of comorbid disease in these IMIDs. Examples of frequently measured pro-inflammatory markers in literature are IL-1, IL-6, TNF-α and CRP.[46] Also adhesion molecules play a role in the inflammatory process, like e-selectin and ICAM. Interleukine-10 is mostly measured as an anti-inflammatory cytokine, which can be decreased in many inflammatory diseases.

Association of comorbidities with psoriasis and inflammatory arthritis

Because of the high disease activity that can affect almost any organ, systemic rheumatoid arthritis (RA) is a well-established independent risk factor for various inflammation related comorbidities including cardiovascular disease. The impact of RA on the cardiovascular risk is even comparable with diabetes and has therefore been added as a risk factor for assessing the cardiovascular risk profile as is used by the Dutch general practitioners cardiovascular risk management guideline (NHG).[47] The systemic inflammation confers an additional risk for cardiovascular mortality, even after controlling for traditional cardiovascular co-morbidities and risk factors.[48] The risk of cardiovascular events is decreased in those RA patients using systemic treatments like TNF inhibitors and MTX.[49]

Also many comorbidities have been associated with psoriasis such as cardiovascular disease, diabetes, NAFLD, Crohn's disease, ulcerative colitis, celiac disease, uveitis, depression, osteoporosis. There might be a small role for a direct effect of inflammation in these associations among those psoriasis patients with severe disease, but it is more likely that most associations are more complex and multifactorial than in RA.[50] For psoriatic arthritis patients this may be somewhat different than for psoriasis patients with joint involvement, as they may have more systemic inflammation. Especially in psoriasis, unhealthy life style factors are often seen, perhaps related to the impaired health related quality of life of this population, resulting in a higher prevalence of comorbidities related to the metabolic syndrome like diabetes. Other explanations for the described comorbidities in psoriasis can be related to therapeutic interventions (like cyclosporine or acitretin) and therefore the overall effect of treating psoriasis on the cardiovascular risk is less clear. [49] Finally, in all comorbidities one should also correct for the overall increased use of medical care leading to detection bias (the more you see a doctor….).

Liver disease

The association between NAFLD and psoriasis was first described in two Italian studies which showed that patients with psoriasis were 1,5 to 3 fold more likely to have NAFLD compared to controls.[51,52] The increased prevalence of NAFLD was explained by unhealthy life style factors and an increased prevalence of metabolic syndrome in psoriasis patients. (Figure 5)

Compared to patients with psoriatic arthritis and rheumatoid arthritis, liver toxicity due to MTX therapy occurs more frequently in patients with psoriasis.[53] In psoriasis the prevalence of MTX-induced liver fibrosis and cirrhosis varies from 5.7%-71,8%, depending on underlying risk factors and comorbidities.[54] In rheumatic arthritis, the prevalence of mild fibrosis is around 15,3% and 1.3% has severe 1.3% fibrosis, in psoriatic arthritis this prevalence is 9.9% and 1.4%, respectively.[55] Besides the increased prevalence of NAFLD related to comorbid disease and systemic treatment, also a twofold increased risk of auto-immune hepatitis has been described in psoriasis patients compared to the general population.[56]

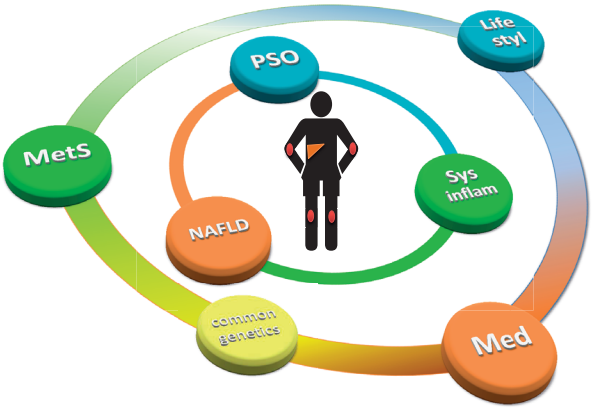

Figure 5. Hepato-psoriatica, the complex association between psoriasis and NAFLD
Abbreviations; pso, psoriasis; MetS, metabolic syndrome; Med, medication; NAFLD, non-alcoholic fatty liver disease; sys inflame, systemic inflammation.

MONITORING LIVER DEVIATIONS IN IMIDS

In patients without systemic treatment

In psoriasis patients without systemic therapy, no standard investigations in monitoring liver disease are recommended. This also holds for psoriatic arthritis and rheumatoid arthritis patients.

Monitoring liver toxicity during MTX use according to different guidelines

MTX is a folic acid antagonist and has anti-inflammatory, immunomodulatory and anti-proliferative mechanisms. Folic acid depended enzyme, e.g dihydrofolaatreduc-

tase, interferes in the DNA and RNA synthesis. The exact working mechanism of MTX is still unknown. MTX was first described by Gubner in 1951 and a FDA approval for psoriasis was given in 1971. Indications for MTX are broad and range from inflammatory skin diseases, to inflammatory joint disease to oncological indications. Minor toxicities due to MTX are common and consist of fatigue, nausea, anorexia and stomatitis. Major toxicities are bone-marrow toxicity, pulmonary fibrosis and hepatotoxicity. To reduce side-effects extra folate intake is advised during MTX treatment.

Risk factors for developing hepatotoxicity are a history of or current moderate to severe alcoholic consumption, persistent liver chemistry deviations in serum, history of hepatitis B or C, family history of inheritable liver disease, history of significant exposure of hepatotoxic drugs or chemicals and components of the metabolic syndrome; diabetes mellitus, obesity and hyperlipidemia.[57]

In the following paragraphs we will describe the guideline advice regarding monitoring for hepatotoxicity during MTX use in psoriasis and inflammatory arthritis and this is also summarized in Table 1.

Table 1. psoriasis and arthritis guideline on methotrexate use.

	Before start (on indication)	During treatment	STOP/ to hepatologist
Dutch dermatology	ALT, GGT, HBV, HCV (HIV, albumine) (P3NP)	ALT, GGT (P3NP)	>3x ↑ ALT or GGT in 6 weeksabnormale P3NP
British dermatology	Liver blood tests, HBV, HCV, P3NP	Liver enzymes, P3NP every 3 month,	liver enzymes >2× baseline values, persistently abnormal P3NP (>4.2 mcg/L in at least 3 samples over a 12-month period or 2 above >8 mcg/L).
European dermatology	Liver enzymes, HBV, HCV, P3NP when available (albumin)	Liver enzymes, P3NP every 3 month, (albumin)	liver enzymes >2× baseline values, persistently abnormal P3NP (>4.2 mcg/L in at least three samples over a 12-month period).
Dutch rheumatology	ALT (HBV, HCV, HIV)	ALT	>3x ↑ ALT

Dutch dermatology guideline:[58]

The Dutch guidelines for psoriasis were the first major evidence-based guidelines to be developed starting in 2003.[59] Since then this guideline has been updated regularly and a new update will take place this year (2017) again. Procollagen-3 N-terminal Peptide (P3NP) is currently recommended to be determined before and during MTX use to monitor for hepatotoxicity. However, in the updated guidelines this recommendation will probably disappear. Before starting MTX the following laboratory values and tests are recommended to monitor for hepatotoxicity: alanine aminotransferase (ALT),

gamma-glutamyltransferase (GGT), hepatitis B virus (HBV), hepatitis C virus (HCV) and when indicated human immunodeficiency virus (HIV) and albumin. During treatment ALT, GGT and serum albumin when suspicion of hypo albumin. When ALT of GGT is more than 3 times elevated, referral to a hepatologist should take place within 6 weeks to perform an ultrasound of the liver or fibroscan or if indicated a liver biopsy. MTX should be discontinued if the liver biopsy shows a Roenigk stadium of Graad IIIB, IV or higher.

British guidelines:[60]
Before starting MTX treatment liver function tests and P3NP should be conducted. The cut-off value for P3PNP is < 4.2. Elevation of P3NP above 8.0 mg/mL should prompt further hepatic investigation. If the value is between 4.2 and 8 mg/mL MTX can be started, but if during treatment values remain increased, referral to a hepatologist is necessary. The routine use of liver biopsy for monitoring MTX hepatotoxicity is no longer recommended in the British guidline.[60]

European guidelines:[61]
P3NP should be tested when available before start and every three month during therapy. When persistently abnormal P3NP (>4.2 mcg/L in at least three samples over a 12-month period), further research or referral to a hepatologist should be done.

Dutch rheumatology guidelines:[62]
The Dutch rheumatology guidelines recommend before starting MTX therapy to test ALT levels. HBV, HCV and HIV should only be tested on indication. During treatment monthly ALT control is advised for the first three months and after dose escalation. When ALT levels are over 3 times elevated MTX should be stopped and after normalization MTX can be reintroduced in a lower dosage. When on lower dosage MTX, ALT elevation is persistent, referral to a hepatologist is recommended.

Monitoring NAFLD/ liver fibrosis

Serum GGT, alkaline phosphatase (ALP), ALT and aspartate aminotransferase (AST) levels are commonly used to monitor liver damage. ALT is predominantly found in the liver, whereas GGT, ALP and AST are expressed in multiple other tissues, including heart, skeletal muscle, kidneys, bone and brain. Elevation of serum liver chemistry tests are reported in up to a quarter of individuals in Western population. The majority of liver test abnormalities may be attributed to the presence of alcoholic and NAFLD.[63] Although elevation of ALT and AST is most frequent caused by NAFLD, they do not discriminate between simple fatty liver, steatohepatitis or fibrosis. Furthermore, up to 50% of NAFLD patients have normal ALT levels[64] and in patients with liver fibrosis and cirrhosis, ALT levels are often within the normal range.[41] Therefore, ALT and AST are apparently poor

diagnostic markers for NAFLD and liver fibrosis and may be used to monitor acute liver toxicity (i.e. drug induced hepatitis), but creates a false sense of security when it comes to monitoring liver fibrosis.

As described previously, P3NP is part of some dermatology guidelines to monitor liver fibrosis during MTX therapy. P3NP is a serum marker for collagen turnover and used as a marker for measuring hepatic fibrosis.[65] Although higher values of P3NP are found in patients with liver fibrosis, P3NP is not organ specific, and can also be elevated by active arthritis, recent bone fracture or recent myocardial infarction, and often has higher values among younger people. Furthermore, P3NP is only of use as a serial measurement. Probably due to these shortcomings, P3NP has been abandoned in hepatology a while ago and will no longer be part of the Dutch psoriasis guideline.

Liver biopsy is the golden standard for staging hepatic fibrosis, inflammatory activity and diagnosing other chronic liver diseases, but it has a lot of disadvantages as a monitoring tool. The procedure is invasive, costly, requires specialized expertise, is limited by its semi-quantitative nature, sample error, intra-observer variability and not at least carries a risk of morbidity and even mortality.[66]

There is a high need for a non-invasive marker to monitor for liver fibrosis in psoriasis patients and other IMIDs, especially during potential hepatotoxic treatment. Different non-invasive methods of liver fibrosis assessment have been identified and widely validated using imaging techniques and serum biomarkers. Although liver biopsy cannot be totally abandoned, these non-invasive techniques reduce the need significantly. One of the most frequently used non-invasive methods is transient elastography (TE).[67] TE measures liver stiffness in a 1 cm wide by 5 cm long volume, which is 100 times greater than a liver biopsy.[68] TE has a high diagnostic accuracy, independent from the underlying liver disease, to predict advanced liver fibrosis.[69] Up to now only two small studies have evaluated TE in patients with psoriasis using high dose MTX.[70,71] TE is reliable to identify advanced stages of fibrosis. A limitation is the need of specialized instruments and expertise, and higher unreliable measurements in obese patients. In daily clinic (for dermatologist, rheumatologist and general practitioners) a serum biomarker is better usable and accessible. Several tests have been developed. The complex direct panels are superior to the indirect and single biomarkers. The Enhanced Liver Fibrosis (ELF) test is a direct complex panel in detecting liver fibrosis. ELF is an algorithm of three biomarkers, P3NP, tissue inhibitor of matrix metalloproteinase 1 (TIMP) and hyaluronic acid (HA). A higher concentration of individual biomarkers leads to a higher ELF score and indicates a greater likelihood of more severe fibrosis. The ELF test has been extensively validated in healthy subjects and multiple liver diseases, e.g. NAFLD, hepatitis B and C, and alcoholic liver disease.[72] The ELF test might be even superior to liver biopsy in predicting

clinical outcome in chronic liver disease.[73] Other strengths are better automaticity, high reproducibility, and less invasiveness.

AIMS OF THIS THESIS

Many comorbidities have been associated with psoriasis, especially related to metabolic syndrome and cardiovascular disease. However, little is known about the association between psoriasis and NAFLD, which are both linked to the metabolic syndrome with its inflammatory components.

The main topic of this thesis is the relation between psoriasis and liver disease. in the first part we focus on systemic inflammation. We start in chapter one with a systemic review and meta analyses on systemic inflammation in psoriasis compared to healthy controls, taking into account the influence of gender, age and disease severity. In the second chapter we put the systemic inflammation of psoriasis patients into a wider perspective and compare this systemic inflammation of psoriasis to psoriatic arthritis and rheumatoid arthritis.

In the second part, we will zoom in on the relation on liver disease within psoriasis patients. In chapter 4 we investigate the prevalence of non-alcoholic fatty liver disease, using ultrasound, in psoriasis subjects compared to the general population in the Rotterdam study correcting for confounding factors. In the following chapter we describe the prevalence of liver fibrosis and cirrhosis, the next stage of liver disease, using the transient elastography (Fibroscan) in the Rotterdam Study in psoriasis compared to the general population. Chapter 6 describes the ELF test as a relative new biomarker in detecting liver fibrosis in psoriasis and inflammatory arthritis. In the last chapter we will focus on the reliability of the ELF test in psoriatic arthritis and rheumatic arthritis in relation to systemic inflammation. Finally we will discuss our findings in the general discussion and provide recommendations for the future.

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