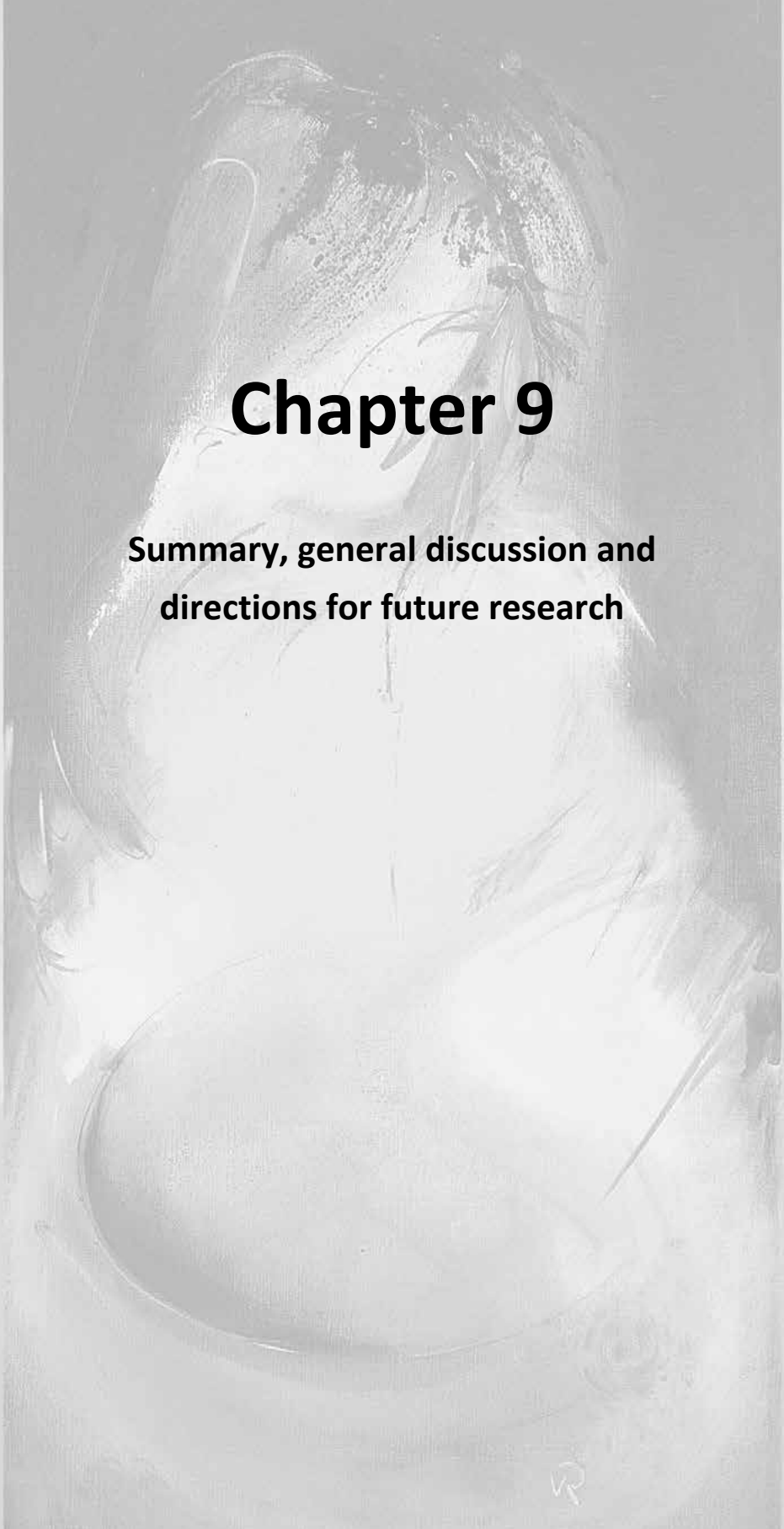

Chapter 9

Summary, general discussion and directions for future research

Summary

Clinical presentation and course of sarcoidosis are both highly variable, depending on several disease and patient characteristics.[1-3] Most sarcoidosis patients show spontaneous resolution, but in patients with a severe disease course and poor prognosis a timely implementation of an appropriate customized individual pharmacological treatment regimen is important to avoid or slow down the development of complications and to alleviate the disease burden.[4,5] Despite the availability of several immunosuppressive therapeutic options in sarcoidosis, standardized management strategies are lacking. The published data on the different pharmacological therapeutics are limited and the treatment therefore remains predominantly empiric.[4,6]

The aim of the studies presented in this thesis was to contribute in the optimization and improvement of pharmacotherapeutic options in sarcoidosis. Several aspects in terms of amelioration of treatment were investigated, with emphasis on the meaning of body composition profiling, the desirable handling of liver test abnormalities, and the development of practical recommendations for the optimal use of methotrexate (MTX) and tumor necrosis factor-alpha (TNF-α) inhibitors in sarcoidosis. Furthermore, possible factors identifying responders to TNF-α inhibitors were explored. Four studies included data from sarcoidosis patients who were referred to a tertiary referral centre in the Netherlands. Two studies evaluated the experience with therapeutic agents amongst sarcoidosis experts worldwide by means of online web-based questionnaires, and combined these data with evidence from the literature. A general overview of the findings from this thesis is subsequently presented.

Overview of main findings

Chapter 1, the general introduction, presents a summary of the pathogenesis, clinical presentation and diagnostic approach of sarcoidosis. Furthermore, it describes the available first-, second-, and third-line therapeutic options in sarcoidosis. Lastly, an outline of the thesis is provided.

Chapter 2 provides an overview of the extent, distribution and consistency of organ involvement detected by fluorine18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT or PET) in 158 sarcoidosis patients with persistent disabling symptoms. Positive PET findings were classified as thoracic and/or extrathoracic. The majority (93%) of sarcoidosis patients had intrathoracic activity (79% mediastinal and 64% pulmonary activity, respectively) and 75% displayed extrathoracic activity (mainly peripheral lymph nodes, bone/bone marrow, and spleen). Hepatic positivity was always accompanied by splenic activity, whereas the majority of patients with parotid gland, splenic or bone/bone marrow activity showed lymph node activity. A substantial number of patients with PET positive pulmonary findings (86%) had signs of respiratory functional impairment. No obvious association between

hepatic, splenic or bone/bone marrow activity and their corresponding laboratory abnormalities suggestive of specific organ involvement, was found. PET can be especially useful in the assessment of extent, distribution and consistency of inflammatory activity in sarcoidosis to provide an explanation for persistent disabling symptoms and/or to provide a suitable location for biopsy.

Chapter 3 reports on the prevalence of muscle atrophy and cachexia in 423 Dutch sarcoidosis patients, and the association of these body composition profiles with sarcoidosis disease activity and severity. Fat-free mass was assessed as an indirect measure of muscle mass by bioelectrical impedance analysis. Patients were stratified based on body mass index (BMI) and fat-free mass index (FFMI). Muscle atrophy was defined as FFMI <15 kg/m^2 for women and <17 kg/m^2 for men corresponding to <10th percentile of current reference values; cachexia as BMI <20 combined with muscle atrophy. Relevant clinical data were gathered retrospectively. Muscle atrophy was present in 25% and cachexia in 5% of sarcoidosis patients. Patients with muscle atrophy showed significantly worse lung function (diffusing capacity for carbon monoxide (DLCO), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), all p values <0.01) and impaired exercise capacity (maximal oxygen uptake (VO_2max), p<0.001). The associations were most pronounced in patients with cachexia. These results demonstrate that muscle atrophy and cachexia are substantial problems in sarcoidosis.

Chapter 4 describes the presence and severity of liver test abnormalities in 837 patients with confirmed sarcoidosis. Additionally, the association between severity of liver test abnormalities and histopathological abnormalities in hepatic sarcoidosis was evaluated. Over a 9-year period, relevant clinical data were gathered from medical records. Liver test abnormalities (alkaline phosphatase, γ-glutamyl transferase, alanine aminotransferase (ALT) or aspartate aminotransferase >1.5 times the upper limit of normal (ULN)) were classified according to severity into mild (zero liver tests ≥3 times the ULN), moderate (one or two liver tests ≥3 times the ULN) and severe (three or four liver tests ≥3 times the ULN). In 24% of the studied patients, liver test abnormalities were present; in 15% highly likely because of hepatic involvement of sarcoidosis. In 22 of this latter group, a liver biopsy was obtained; 21 biopsies were compatible with hepatic sarcoidosis. The presence and degree of inflammation, fibrosis, and the distribution of granulomas in these liver biopsies were examined. Moderate and severe liver test abnormalities were associated with more advanced histopathological disease. In the management of hepatic sarcoidosis, for patients with moderate or severe liver test abnormalities a liver biopsy is recommended.

Chapter 5 provides an overview of the knowledge available in the literature about therapeutic options for sarcoidosis liver involvement, and combines these data into recommendations for the optimal therapeutic approach in clinical practice. Only 5–30% of patients with hepatic sarcoidosis display symptoms. Nevertheless, in some cases hepatic sarcoidosis can have a rapid progressive course with serious complications, which stresses the importance of an appropriate and carefully timed therapeutic

approach. Because symptomatic hepatic sarcoidosis is uncommon, therapeutic studies are scarce. Data regarding when to initiate which treatment regimen are lacking. Case reports describe beneficial effects of glucocorticosteroids and the augmentation with cytotoxic and/or TNF-α inhibitor therapy. However, because of small sample sizes, no meaningful conclusions can be drawn. In symptomatic hepatic sarcoidosis patients, it is recommended to start pharmacotherapy with glucocorticosteroids, preceded by ursodeoxycholic acid when signs of cholestasis disease are present. Furthermore, antioxidants can be considered. In refractory cases or when glucocorticosteroid weaning is impossible, cytotoxic drugs or TNF-α inhibitors should be considered. However, there is a need for future studies to assess the effect of treatment on disease progression and complications in hepatic sarcoidosis.

Chapter 6 presents the development of practical recommendations, on behalf of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), for the use of methotrexate (MTX) in sarcoidosis by integrating the evidence obtained through a systematic literature review and the opinions of sarcoidosis experts worldwide. The literature search identified 237 papers, 43 of which were included. Randomized controlled trial (RCT) evidence supporting the use of MTX in sarcoidosis was limited. An online survey concerning 10 clinical questions was sent through the WASOG newsletter to the experts. Forty-five per cent (113 of 250) of the sarcoidosis experts contacted, completed the survey (Europe 55%, North America 26%, and Asia 12%). Ten recommendations were formulated concerning the indications for use, starting dose, folic acid, work-up, contraindications, monitoring, administration options in case of adverse gastrointestinal effects, hepatotoxicity, long-term safety and use during pregnancy and breast feeding. The mean level of agreement for the total set of recommendations amongst the leading sarcoidologists was high (8.7, range 8.0–10). Furthermore, a mobile application (app) was developed for smartphone or tablet with these recommendations including some clinical sarcoidosis cases (Appendix 2). The app ‘MTX in sarcoidosis’ can be downloaded for free in the Apple Store or Google Play Store.

Chapter 7 describes the development of practical recommendations for the use of the TNF-α inhibitors infliximab and adalimumab in the treatment of refractory sarcoidosis. Evidence obtained from a literature search was combined with the results of a Delphi method of polling amongst sarcoidosis experts worldwide. The literature search identified 256 papers, 101 of which were included. RCTs about the use of TNF-α inhibitors in sarcoidosis are limited. Studies conducted in sarcoidosis were supplemented with data obtained from relevant studies in other inflammatory diseases. An online survey addressing 12 clinical questions was performed amongst 20 of the world’s leading sarcoidologists to investigate consensus in case of inadequate data to determine an objective answer. Ninety-five per cent (19 of 20) of the sarcoidosis experts contacted completed the survey (Europe 68%, North America 32%). Nine recommendations were formulated concerning general aspects of TNF-α inhibitor use. Furthermore, specific sarcoidosis related items, including indications, starting and

maintenance dosage, interval of treatment, treatment duration, and discontinuation regimen of infliximab and adalimumab, were also addressed. The recommendations intend to support the clinician in the management of refractory sarcoidosis patients.

In sarcoidosis, the presence of the GG-genotype of *TNF-α* G-308A polymorphism has been associated with poor prognosis.[7] **Chapter 8** assesses the association between the presence of the *TNF-α* G-308A polymorphism and the response to anti-TNF-α therapy amongst 111 patients with refractory sarcoidosis. The included patients were followed for at least 12 months after the initiation of infliximab (n=76) or adalimumab (n=35). Main symptoms in these patients were small fiber neuropathy (82%), pulmonary involvement (62%), uveitis (28%) and/or fatigue (90%). Patients were genotyped for the presence of the *TNF-α* G-308A polymorphism. Treatment response was assessed using clinical outcome measures and questionnaires. Of the total group of patients receiving TNF-α inhibitors, 75% responded well. Of the patients with the GG-genotype of *TNF-α* G-308A polymorphism 93.6% (73/78; p<0.001) improved, while only 30.3% (10/33) of the *TNF-α* -308A variant allele carriers responded favorably to the TNF-α inhibitor. Sarcoidosis patients without the *TNF-α* -308A variant allele (GG-genotype) had a three-fold higher probability of response to TNF-α inhibitors. Further research is needed to evaluate the value of genotyping for the *TNF-α* G-308A polymorphism in order to customize and tailor TNF-α inhibitor treatment.

Highlights of this thesis

In conclusion, this thesis presents several aspects regarding optimization of pharmacotherapeutic options in sarcoidosis. First of all, cachexia and muscle atrophy are frequent problems in sarcoidosis and are associated with more severe pulmonary disease. These findings indicate the importance of considering body composition profiling in the management of sarcoidosis. Furthermore, in a substantial proportion (24%) of sarcoidosis patients liver test abnormalities are present. In the majority, these abnormalities are probably associated with hepatic sarcoidosis. However, other causes should be excluded. When moderate or severe liver test abnormalities are present in probable hepatic sarcoidosis, a liver biopsy should be considered, since advanced histopathological disease is likely. The biopsy findings can be used in establishing an adequate therapeutic strategy of hepatic sarcoidosis, for which recommendations are presented in this thesis. Moreover, multinational recommendations for the use of MTX and TNF-α inhibitors are provided, based on findings from the literature combined with the opinions of sarcoidosis experts worldwide. Finally, the finding that sarcoidosis patients without the *TNF-α* -308A variant allele (GG-genotype) have a three-fold higher probability of response to TNF-α inhibitors compared with *TNF-α* -308A variant allele carriers (GA- or AA-genotype), indicates a possible role for genotyping for the *TNF-α* G-308A polymorphism in order to tailor anti-TNF-α treatment. However, future research is needed to evaluate possible factors identifying responders to TNF-α inhibitors and to assess the role for *TNF-α* G-308A genotyping in this process.

General discussion

Optimization of the pharmacotherapeutic management of sarcoidosis is important and of great clinical relevance. Since sarcoidosis can present to any one of a variety of (organ) specialists, therapeutic decisions are dependent on the individual specialist's expertise. Application of pharmacotherapeutic options by inexperienced physicians can be improved by guidance consisting of therapeutic recommendations. A key issue of treatment must be the avoidance of unnecessary exposure of patients to consecutive pharmacological agents. Furthermore, a multidisciplinary approach is crucial, in which physicians develop a treatment regime after mutual consultation and in cooperation with the patient. The role for the patient in disease management becomes increasingly important. Pursuing personalized medicine is another major aspect in the optimization of therapeutic options. The meaning and implications of the different aspects presented in this thesis will be discussed subsequently.

^{18}F-FDG PET/CT, body composition profiling and liver test abnormalities in sarcoidosis disease management

PET can be very helpful in sarcoidosis disease management and monitoring in several situations.[8,9] One important function is the assessment of sarcoidosis activity, especially when routine diagnostic methods do not provide an explanation for disease related symptoms.[10,11] Besides the assessment of sarcoidosis activity, depicting disease extent and severity is of great clinical relevance, as illustrated in chapter 2.[12] Evaluation of the extent of disease can be helpful to explain persistent disabling (mainly extrathoracic) symptoms.[13] Furthermore, it can support in the decision whether pharmacological therapy should be started and sometimes guide what drug regimen should be chosen.

As in other chronic diseases,[14-17] muscle atrophy and cachexia were shown to be common problems in sarcoidosis (chapter 3).[18] Therefore, considering body composition profiling in the management of sarcoidosis is important. Future research is necessary to assess the effect of a multidisciplinary rehabilitation program on muscle maintenance. Considering body composition is furthermore important in pharmacotherapeutic management. Drug dosing should among others be based on body weight and composition. Cachexia and wasting of chronic disease, for example, can lead to altered drugs pharmacokinetics and -dynamics.[19]

Liver test abnormalities are a frequently encountered problem in sarcoidosis, for which guidance is presented in chapter 4, 5 and 6.[20-22] Liver test abnormalities in sarcoidosis can be the result of hepatic sarcoidosis itself, another (liver) disease or drug toxicity. The degree and type of liver test abnormalities cannot distinguish between these different causes.[23] When abnormal values are present before the start of therapy, hepatic sarcoidosis is a likely cause.[20,23,24] When they develop after the start of an agent with potential hepatic adverse effects, liver test abnormalities are most likely the result

of drug toxicity. Treatment with an anti-inflammatory agent in hepatic sarcoidosis can actually lead to improvement of liver test abnormalities.[25,26]

Glucocorticosteroids in sarcoidosis

In sarcoidosis clinical practice, glucocorticosteroids are the cornerstone therapeutic agent.[3,6,27,28] They have a positive short-term effect on lung function and symptoms, but their beneficial long-term effect remains uncertain.[29] Prolonged use is associated with significant side-effects, such as weight gain, diabetes mellitus, osteoporosis, or striae distensae of the skin (Figure 9.1), making glucocorticosteroids undesirable for chronic disease management.[3,27,30] Another important issue is the presence of glucocorticosteroid resistance, which complicates the treatment of several inflammatory diseases (including chronic obstructive pulmonary disease, asthma, rheumatoid arthritis and Crohn's disease), while the risks of side-effects persist.[31,32] It is not only a problem in severe, but also in mild disease, often leading to the prescription of high steroid dosages without beneficial effect.[31] Several molecular mechanisms of resistance have been identified. One factor is genetic susceptibility to steroid resistance due to different polymorphisms in different genes, a finding which can possibly contribute towards personalized therapy.[31,33,34] Furthermore, interference with the steroid response by constitutive epithelial activation of pro-inflammatory mediators, including nuclear factor-kappa B (NF-kB), resulting in inhibition of glucocorticosteroid receptor transcriptional activity, is another possible mechanism.[31-33] NF-kB activation is shown to be increased in sarcoidosis[35-37] and its suppression by glucocorticosteroids seems less successful than the suppression of angiotensin-converting enzyme activity,[36] indicating that glucocorticosteroid resistance is likely to be an important problem in sarcoidosis as well. When considering the limitations we are aware of nowadays, registration approval would be questionable if glucocorticosteroids were to be introduced at present.

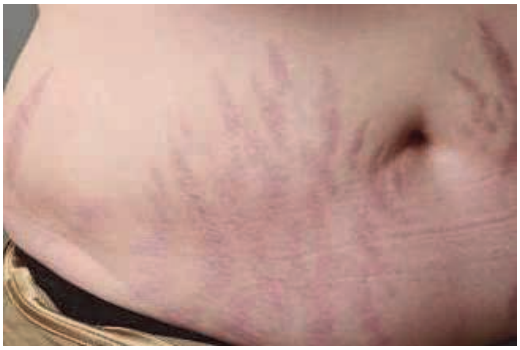

Figure 9.1 Extensive striae distensae of the skin in a young woman with sarcoidosis after 3 months of treatment with glucocorticosteroids because of uveitis.

Methotrexate in sarcoidosis

In steroid-refractory cases and in the presence of steroid-associated side-effects, second-line or disease-modifying antisarcoid drugs (DMASDs), with usually steroid-sparing potency, are available.[3,6,27,38,39] MTX is the central drug in the pharmacotherapeutic management of rheumatoid arthritis and other immune mediated inflammatory diseases.[40,41] In pulmonary sarcoidosis, the glucocorticosteroid-sparing potency of MTX has been demonstrated (Figure 9.2).[42] Sarcoidosis experts consider MTX the first-choice DMASD.[43] Unfortunately, the evidence to support the use of MTX in sarcoidosis is limited. Therefore, evidence extrapolated from studies in rheumatic inflammatory diseases and the expert opinions of sarcoidologists worldwide were used to help develop the MTX recommendations presented in chapter 6.[22] The broad range of participants should enhance the implementation of the recommendations in sarcoidosis practice. Their value is further strengthened by the high level of agreement amongst the world's leading experts. Nevertheless, due to the limited available high-quality studies, the recommendations lack in strength.

Inexperience among individual specialists can lead to suboptimal use of MTX. Especially at two specific points, progress can be made. Primarily, as discussed in chapter 6, a substantial part of sarcoidosis experts (11%) did not prescribe MTX in sarcoidosis. The predominant reason consisted of fear for toxicity (70%). However, experienced respondents reported MTX discontinuation because of side-effects in only 10% of the cases. Sarcoidosis case reports show even lower discontinuation rates.[42,45] This finding is in line with rheumatoid arthritis studies, showing that withdrawals of MTX due to toxicity are less common than for most other DMARDs.[46]

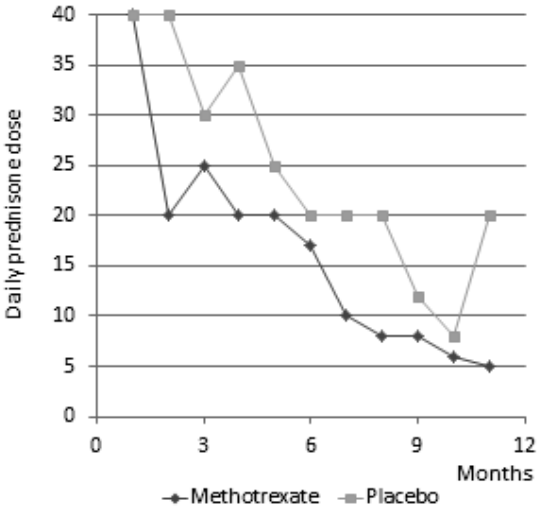

Figure 9.2 Average prednisone dosage at various time intervals for patients with acute pulmonary sarcoidosis receiving either placebo or methotrexate. There was a significant difference in the average prednisone dose after 6 months of therapy. Adapted from Baughman et al.[42,44]

A retrospective study performed in a large group of 607 sarcoidosis patients on MTX treatment and with evaluable blood work (Sarcoidosis Clinic at the University of Cincinnati Medical Centre, Cincinnati, Ohio, USA), investigated the occurrence of total and severe leucocytopenia respectively (defined as white blood cell (WBC) count <3.8*10^3/µl and <1.5*10^3/µl); and total and severe liver test abnormalities respectively (ALT >1.5x the upper limit of normal (ULN) and >3x ULN). Leucocytopenia was present in 11.9%, severe leucocytopenia in 0.2%, liver test abnormalities in 12.8% and severe liver test abnormalities in 1.6% of these patients. The results show that the occurrence of severe MTX-induced bone marrow or liver toxicity was low (unpublished data). In rheumatoid arthritis, long-term MTX use is not associated with an increased risk of serious infections.[46-48] Recently, a meta-analysis in rheumatoid arthritis showed that MTX was associated with a small increased risk of respiratory infections (RR 1.11, 95% CI 1.02-1.21), without an increased risk of non-infectious respiratory events or pulmonary death compared to other DMASDs and biological agents, suggesting a lower risk than previously believed.[49] There is no strong evidence for the development of malignancies during MTX use.[46] A low risk of developing Epstein-Barr virus-related lymphoma has been suggested following exposure to MTX.[46,47,50,51] A recent study in Japan indeed suggests that MTX is an independent risk factor for EBV-related lymphoproliferative disorders in rheumatoid arthritis patients, but further evidence still is required.[52] Based on an acceptable safety profile, it can be said that MTX is appropriate for short- and long-term use in most patients. Fear for MTX among physicians often seems to be based on inexperience. The recommendations can serve to provide more guidance to MTX therapy in sarcoidosis.

When considering gastrointestinal MTX intolerance, a recently developed questionnaire can be used to assess symptoms occurring before and after MTX administration. Studies in several rheumatic inflammatory diseases show that besides gastrointestinal symptoms after MTX, patients also experience these symptoms prior to and when thinking of MTX intake. Therefore, patients on MTX should be closely monitored for early detection of MTX intolerance, in order to intervene timely and avoid discontinuation of an effective treatment.[53,54] Less than 50% of experienced sarcoidosis experts are aware of the possibilities of parenteral administration or splitting of the oral dose in case of MTX-induced gastrointestinal side-effects. In rheumatoid arthritis, parenteral administration is reported to have more efficacy, which can be explained by a higher bioavailability.[55,56] Splitting the oral dose can lead to a higher efficacy of especially higher oral dosages, due to a limited absorption from the gastrointestinal tract when the dosage is ingested at once.[57,58] Both methods can lead to less gastrointestinal toxicity, as illustrated in Figure 9.3. Before discontinuing MTX in case of insufficient response or gastrointestinal side-effects, it is important to consider these aspects.

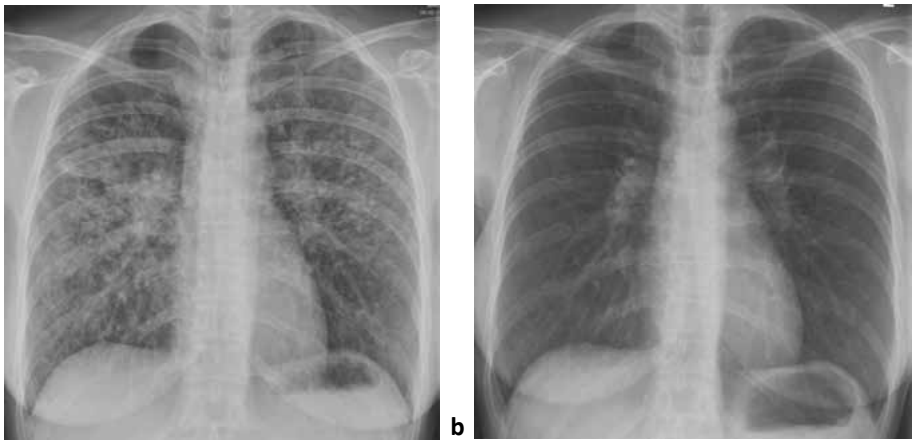

Figure 9.3 A 38-year-old woman had a 1-year history of biopsy-proven sarcoidosis. She had been previously treated with oral prednisone, starting at 40 mg daily, because of respiratory functional impairment, fatigue, exercise intolerance and signs of inflammatory activity (soluble-interleukin2-receptor was 3117 pg/mL, normal range 0-2500 pg/ml). However, no improvement was achieved, so methotrexate (MTX) was started at 12.5 mg once a week orally, together with folic acid 5 mg twice a week. Additionally, treatment with prednisone was tapered off to 7.5 mg daily. Due to gastrointestinal side-effects – mainly nausea – after MTX initiation, the administration of MTX 12.5 mg once a week was changed from oral to subcutaneous. **a.** Chest radiograph before treatment with subcutaneous MTX showed both lymphadenopathy and multiple parenchymal infiltrates. **b.** Chest radiograph after 5 months of treatment with subcutaneous MTX showed substantial improvement. Patient also reported significant clinical improvement after treatment with subcutaneous MTX.

TNF-α inhibitors in sarcoidosis

In some sarcoidosis patients, the available first- and second-line therapeutics do not provide a solution, despite their optimized application. The potent pro-inflammatory TNF-α plays a critical role in the immunopathogenesis of sarcoidosis by regulating and sustaining granuloma formation.[2,59-61] In refractory cases, biological TNF-α inhibitors have therefore been introduced as third-line treatment options.[6,27] Studies investigating the use of infliximab and adalimumab in sarcoidosis are limited, but have shown good results with regard to short-term efficacy.[62-76] Chapter 8 also shows the effectiveness of infliximab and adalimumab in treating different disease manifestations of refractory sarcoidosis (Figure 9.4).[77] To date, etanercept has not been proven effective in sarcoidosis disease management.[78,79] Since the costs of TNF-α inhibitors are considerable and substantial side-effects are reported, optimal use is important.[80-82] Sarcoidosis patients are in general treated by pulmonologists with usually less TNF-α inhibitor treatment experience. Moreover, evidence-based recommendations for infliximab and adalimumab therapy in sarcoidosis are lacking. Therefore, recommendations are needed to support the clinician in the use of TNF-α inhibitors, which are presented in chapter 7.[83] Given the limited available evidence in sarcoidosis, a Delphi method of polling to investigate consensus amongst sarcoidosis experts worldwide and data obtained from relevant studies in other inflammatory diseases were used to supplement possible lacunas.

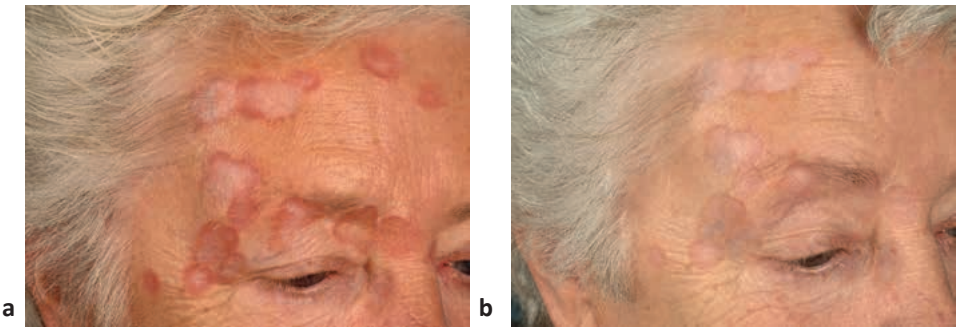

Figure 9.4 An example of a patient with skin manifestations. Photographs taken before (**a**), and after (**b**) 1 year of treatment with infliximab, showing a reduction of the intensity of the facial skin lesions.

As discussed in chapter 7, an approach specific for sarcoidosis is essential when initiating TNF-α inhibitor therapy. Experts in the field noticed that special attention should be paid to starting and maintenance dosages, interval and duration of treatment, and discontinuation regimens. The recommendations differ from regimens used in other inflammatory diseases, but are solely based on eminence- and experienced-based medicine. Therefore, future RCTs are necessary to investigate

aspects such as the long-term effectiveness of TNF-α inhibitors in sarcoidosis; their use in different disease manifestations, including cardiac sarcoidosis; the comparison of different starting dosages, maintenance dosages and treatment intervals of infliximab and adalimumab respectively; and the optimal discontinuation regimen for infliximab and adalimumab to achieve 'biological free remission' (BFR), i.e. sustainability of remission after a biological agent is discontinued.

A difficult issue is discontinuation of TNF-α inhibitor treatment in stable disease. The first challenge is the identification of patients with stabilization of sarcoidosis disease, i.e. patients who might be possible candidates for sustained BFR after tapering down or stopping TNF-α inhibitor treatment. To identify stable disease, exact defined response criteria are necessary.[84] Defining treatment response in sarcoidosis is difficult, since organ involvement and disease course may well be unpredictable. In chapter 8, we made a first attempt.[77] Prospective studies are needed to establish criteria for the identification of responders and non-responders when evaluating pharmacological treatment. Another difficulty is the establishment of the optimal period before successful withdrawal of TNF-α inhibitors is reasonable and of the indicators which can be used to ascertain this period. Vorselaars et al.[85] showed that the majority of sarcoidosis patients (29/47, 62%) relapsed after discontinuation of infliximab after a mean treatment duration of 8.5 months. Future research is necessary to establish in which sarcoidosis patients and after what treatment duration, sustained BFR can be achieved, if this is an achievable goal at all.

Pharmacogenetics in sarcoidosis

Pharmacogenetics may provide an objective explanation for the discrepancies observed in response to pharmacotherapeutic agents amongst sarcoidosis patients.[86] The genetic characteristics of the patient might interact with a certain drug, affecting its pharmacological action and ultimately leading to different treatment effects and toxicity risks.[86] The principles of pharmacogenetics can potentially be applied to optimize pharmacological treatment. 'Gene chips' with a person's polymorphic genotype may be used, combined with characteristics of disease phenotype or appearance in the individual patient, to personalize drug treatment.[87,88] Choosing the drug of most benefit for a particular patient would avoid unnecessary exposures to potentially toxic drugs and would lead to more effective, cheaper and faster disease control.[86]

Genetic analysis has previously revealed a number of polymorphisms in genes coding for TNF-α, with potential functional consequences.[89] These polymorphisms might play a role in the clinical and prognostic diversity of sarcoidosis. The variant A-allele of the *TNF-α* G-308A gene (GA- or AA-genotype) is more frequently observed in patients with Löfgren's syndrome, an acute form of sarcoidosis with often spontaneous remission.[89-93] The risk of progression to a more severe or persistent pulmonary disease course was found to be higher in patients without the *TNF-α* -308A variant allele (GG-

genotype).[7] In addition to the *TNF-α* G-308A polymorphism, the *TNF-α* G-234A and *LTA NcoI* A252G polymorphisms were also suggested to have a possible role in sarcoidosis disease course.[89,91,94] Furthermore, human leukocyte antigen (HLA)-DRB1*03 has been associated with a favorable prognosis.[7,90] Because of the strong linkage between *TNF-α* G-308A and HLA-DRB1*03, genotyping of one simple and less expensive TNF-α single nucleotide polymorphism can be used to predict the prognosis of sarcoidosis in clinical practice.[7,90]

The *TNF-α* G-308A polymorphism has been studied quite extensively in relation to prediction of TNF-α inhibitor treatment response in rheumatoid arthritis. Absence of the *TNF-α* -308A variant allele was found to be associated with better response, suggesting a contribution of *TNF-α* G-308A polymorphism genotyping to the optimized use and distribution of available pharmacological sources.[95-99] Chapter 8 of this thesis also shows a possible role for *TNF-α* G-308A polymorphism genotyping when tailoring TNF-α inhibitor therapy in sarcoidosis.[77] However, the exact implications need to be evaluated, as well as other possible (genetic) factors identifying responders to TNF-α inhibitors.

In rheumatic inflammatory diseases, the value of polymorphism genotyping has also been studied to predict response to other therapeutic agents. For MTX genetics, studies have struggled to obtain consistent, replicable results.[86] Several polymorphisms and genetic patterns have been investigated. Evidence suggests for example a favorable response in reduced folate carrier 1 (*RFC1*) G80A variant allele carriers.[86,100,101] A recent meta-analysis showed that the odds of MTX efficacy increased by 42% for those with the *RFC1* 80AA-genotype compared to carriers of the wild type G allele (AA- versus AG/GG-genotype).[102] Furthermore, many polymorphisms have been described for the methylenetetrahydrofolate reductase (*MTHFR*) gene.[87,103] Of these, the C677T and A1298C polymorphisms have been associated with different toxicity or response effects to MTX therapy.[87,103-105] HLA-DRB1 shared epitope-positive patients seem to respond worse to MTX, especially carriers of the HLA-DRB1*04 allele.[86,106,107] In sarcoidosis, the value of polymorphism genotyping when tailoring MTX treatment, but also other agents, needs to be explored. In the most ideal situation, more insight into the influence of genetic variables on drug effectiveness and toxicity could lead to a more appropriate therapeutic choice, obviating a possibly unnecessary switch to other potentially less effective second-line alternatives or to more costly biologicals.[86]

Directions for future research

This thesis is an attempt to optimize pharmacotherapeutic options in sarcoidosis. Future research should focus on several other aspects to further improve management of sarcoidosis. Recommendations for MTX and TNF-α inhibitors in sarcoidosis are provided herein. Despite the fact that glucocorticosteroids are the first-line treatment option and are most commonly prescribed, guidelines for their use in sarcoidosis are

not available. Furthermore, standardized management strategies for the use of other DMASDs, such as azathioprine or leflunomide, are lacking. The first step for future research should consist of the development of recommendations for the use of glucocorticosteroids and DMASDs in sarcoidosis, based on available evidence and combined with expert consensus if necessary, to supplement the guidance provided in this thesis.

Glucocorticosteroid resistance is an important issue of research in other inflammatory diseases. Until recently, therapy consisted of switching to alternative anti-inflammatory agents. However, many different molecular mechanisms of glucocorticoid resistance have now been elucidated, which can lead to new therapeutic strategies in the future, including the reversal of glucocorticoid resistance by blocking its underlying mechanisms. In sarcoidosis, the issue of resistance and its management needs to be evaluated.

In sarcoidosis, glucocorticosteroids and DMASDs are used for many years. Nevertheless, the RCT evidence supporting their use is limited. Most data come from observational case series. Treatment remains therefore predominantly empiric or is based on expert opinion.[4,6] RCTs studying the effects of the different immunosuppressive agents on exact defined outcome measures for various disease manifestations and with a reasonable duration of follow-up to establish both short- and long-term efficacy, are necessary. Using defined endpoints and response criteria enables comparison of different DMASDs and comparison between different studies. Prospective RCTs are needed to establish criteria for the identification of responders and non-responders and can contribute to the improvement of current treatment strategies.

Recent studies support the use of new experimental treatment agents as alternative third-line therapy. Rituximab, inhaled vasoactive intestinal peptide and apremilast have been investigated.[108-114] Abatacept en tocilizumab have been successfully used in rheumatoid arthritis.[115,116] Regarding their immunopharmacological mode of action, one might consider them as promising in sarcoidosis as well. Future research is necessary to further explore these possibilities. New insights into sarcoidosis pathogenesis, can find other new possible drug targets. Fatigue and small fiber neuropathy, which are devastating problems in sarcoidosis, do not always respond to the 'standard' treatment strategies. New experimental treatment modalities have shown promising results in case series and/or pilot studies.[117-120] Future research specifically addressing management of these problems is important.

Potentially, the principles of pharmacogenetics can be applied to optimize pharmacological treatment. This thesis made a first attempt to predict response to TNF-α inhibitors. As mentioned before, further research is needed to evaluate other possible factors and genetic polymorphisms identifying responders to TNF-α inhibitors and to assess the role for *TNF-α* G-308A genotyping in this process. Also when tailoring other therapeutic agents, the value of pharmacogenetics including polymorphism genotyping needs to be explored. Furthermore, if specific patient and disease

characteristics can possibly predict response to available therapy in sarcoidosis is practically unknown. The existence and value of these clinical predictors of response need to be explored. A better understanding of which patients will respond to therapy or develop toxicity based on the genetic and phenotypic characteristics, can prevent an unnecessary switch from one pharmacological agent to another. More insight could lead to both cost reduction and safer, more effective control of the disease, or in other words, help to pursue personalized medicine for the individual patient.

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