Summary
Idiopathic inflammatory myopathies (IIMs) are characterised by progressive muscle weakness and signs of inflammation in the skeletal muscle tissue. The IIMs comprise three main disorders: polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (s-IBM), which differ in their clinical and histopathological features, and in their prognosis. The distinction between PM, DM and s-IBM is therefore of paramount importance, both in daily clinical practice and for research purposes.

Long-term outcome and prognostic factors in PM and DM are still not well known. The use of old classification criteria, not excluding s-IBM, may have led to the inclusion of a heterogeneous group of patients and as a result different outcomes.

In this thesis we focused on: 1) the delineation of the different groups of inflammatory myopathies, s-IBM excluded; 2) genetic factors as risk markers for the different IIMs; and 3) clinical outcome and prognostic factors in well-defined categories of IIM patients.

Since its first description in 1887 by Wagner and Unverricht,¹,² there has been much debate about the diagnostic entity of PM. In the reports of these authors, all patients had skin abnormalities in addition to muscle weakness. Therefore the term dermatomyositis was introduced, but meanwhile the terms polymyositis and dermatomyositis were used interchangeably and for decades it was assumed that dermal lesions were always part of PM. In chapter 2 we reviewed the history of the status of PM.

We investigated the applicability of the most recently developed clinical and histopathological criteria for the diagnostic evaluation of PM and DM in chapter 3. In a retrospective follow-up study in 165 patients with: 1) a previous diagnosis of myositis; 2) a subacute onset of symmetrical, proximal weakness; 3) who presented between 1977 and 1998; and 4) in whom other neuromuscular disorders were excluded, we re-evaluated the diagnosis of myositis.

The diagnoses at presentation, based on clinical, laboratory and histopathological criteria were: PM 9 (overall 5%), DM 59 (overall 36%; 54 isolated DM patients, three DM patients with associated connective tissue disease (CTD), two DM patients with associated malignancy), unspecified myositis (perimysial/perivascular infiltrates, no prominent endomysial cell infiltrates or skin lesions) 65 (overall 39%; 38 isolated unspecified myositis patients, 26 unspecified myositis patients with associated CTD, one patient had unspecified myositis with malignancy), possible myositis (necrotising myopathy, no inflammatory cell infiltrates) 32 (overall 19%; 29 isolated possible myositis patients, three possible myositis patients with associated CTD).

At follow-up, 5 of the 9 PM patients appeared to have typical s-IBM features and in particular prominent distal muscle weakness. None of the remaining 4 patients had the typical picture of PM, i.e. weakness with a limb-girdle distribution. Ten of the 38 patients
with isolated unspecified myositis had developed a CTD. Six percent of the patients with isolated unspecified or possible myositis developed a malignancy after onset of the myositis. We concluded that PM appears to be an extremely rare disease entity and that more than half of the patients with autoimmune myositis can not be diagnosed as PM or DM and has to be considered as unspecified or possible myositis. Secondly, in patients with isolated unspecified myositis one should remain cautious about the development of a CTD. Finally, a workup for diagnosing malignancies should not be limited to patients with DM but also should include patients suffering from isolated unspecified and isolated possible myositis.

In chapter 4 we analysed a specific subgroup of patients with myositis in which the biopsy specimen shows a necrotising myopathy (described as possible myositis in chapter 3). Mononuclear cell infiltrates in the muscle biopsy are the diagnostic hallmark in patients with subacute muscle weakness who are suspected to suffer from an IIM. In patients with the typical clinical features of IIM, absence of these diagnostic mononuclear infiltrates in the muscle biopsy specimen casts doubt on the diagnosis and leads to therapeutic uncertainty.

In this study we described eight patients (five men, three women, range 40-69 years) with subacute severe, symmetrical proximal weakness who had no skin abnormalities compatible with a diagnosis of dermatomyositis. Serum creatine kinase activity was more than 10 times elevated. Repeated muscle biopsy specimens, taken from a symptomatic muscle prior to immunosuppressive treatment showed widespread necrosis, regeneration, and atrophy of muscle fibers, but no significant mononuclear cell infiltrates. Other known causes of necrotising myopathy were excluded. Three patients had a malignancy. Adequately dosed and sustained immunosuppressive treatment eventually resulted in normal or near normal muscle strength in seven patients. It is important to realise that occasionally, patients who clinically present as an IIM may lack mononuclear cell infiltrates in their muscle biopsy specimen. This subacute-onset, progressive necrotising myopathy should not deter the clinician from timely and appropriate treatment as we consider this myopathy to be a subgroup of the steroid-responsive immune-mediated IIMs. Finally, patients with a necrotising myopathy should be screened for underlying malignancies.

In chapter 3 we described that most of the patients with a clinical diagnosis of PM (i.e., subacute-onset of proximal muscle weakness without skin abnormalities) showed perivascular mononuclear cell infiltrates located at perimysial sites in their muscle biopsy specimen, similar to the histopathological findings in DM. We suggested the term unspecified myositis to differentiate it from PM showing endomysial located infiltrates of T cells.

A characteristic finding early in the disease process of DM is the presence of microtubular inclusions in endothelial cells at the ultrastructural level. Early capillary injury preceding muscle damage is the fundamental element of the vascular hypothesis in DM. The observation that most of the patients with unspecified myositis show histopathological
features similar to DM, suggests that microvasculopathy may be also be the underlying pathogenesis in unspecified myositis. Microtubular inclusions in muscle capillaries are not described as a histopathological feature of unspecified myositis, and therefore we searched for this feature in muscle biopsies of patients with unspecified myositis to corroborate our vascular hypothesis in chapter 5. Our study has included muscle biopsies from 20 patients with unspecified myositis with or without a co-existing CTD which were compared to muscle biopsies from 10 patients with DM and from 5 patients with s-IBM. Microtubular inclusions were found in 4 unspecified myositis patients (20%), in 4 DM patients (40%) and in none of the s-IBM patients. All of the unspecified myositis patients with microtubular inclusions had signs and symptoms of another CTD. Our results show that tubuloreticular structures in endothelial cells of muscle capillaries do not only occur in DM, but also in unspecified myositis, especially when there are also signs of CTD. This supports the hypothesis that patients with DM and unspecified myositis share an immune-mediated injury of the muscle microvasculature. Whether our results also represent differences in pathogenesis between unspecified myositis with and without CTD remains to be elucidated.

Genetic factors may contribute to the development of IIMs, although the findings are not consistent and seem to differ between various ethno-geographic populations. Leukocyte IgG receptors (FcγR) serve as a link between the humoral and cellular branches of the immune system. The FcγRs confer potent cellular effector functions to the specificity of antibody and are crucial for immune complex (IC) clearance and antibody-mediated cytotoxicity. The vigour of the inflammatory response following FcγR engagement by immune complexes is determined by the efficacy of the IgG- FcγR interaction. This efficacy of IgG- FcγR interaction shows interindividual variability, due to functional polymorphisms of three FcγR subclasses, i.e. FcγRIIA (R131 vs. H131), FcγRIIIB (V158 vs. F158), and FcγRIIIB (NA1 vs. NA2). Recently, FcγR polymorphisms were found to be associated with disease susceptibility and disease severity of several autoimmune diseases. In chapter 6 we investigated the relevance of FcγR polymorphisms for IIM susceptibility in a large group of Dutch patients. FcγRIIa and FcγRIIIb genotype distributions among IIM, unspecified myositis/DM, and s-IBM patients did not differ significantly from those in controls. However, FcγRIIa genotypes were differentially distributed among 100 IIM patients as compared to 514 healthy controls with a significant increase of the FcγRIIa-V158 genotype. Odds ratios increased by the addition of each FcγRIIa-V158 allele, in particular among patients with unspecified myositis and DM. We concluded that the FcγRIIa-V158 allele may be a possible genetic risk marker for myositis.

In chapter 7 we investigated long-term outcome parameters in a well-characterised group of myositis patients based upon the classification described in chapter 3. We determined mortality, clinical outcome (muscle strength, disability, persistent use of medication and
quality of life), course of disease, and we analysed the prognostic outcome factors. Disease-related death occurred in at least 10% of the patients, mainly because of IIM associated malignancy and pulmonary complications. Re-examination of 110 patients after a median follow-up of five years showed that 20% of the patients remained in remission and were off medication, whereas 80% of the patients showed a polycyclic or chronic continuous course of the disease. The cumulative risk of incident CTD in patients with unspecified myositis was 33% at 7 years. Sixty-five percent of the patients had normal strength at follow-up, 34% had no or slight disability (Rankin 0-1) and 16% had normal physical Sickness Impact Profile scores. Muscle weakness was associated with age > 60 years (OR 3.6, 95% CI 1.3-10.3). Disability was associated with male sex (OR 3.1, 95% CI 1.2-7.9). Forty-one percent of patients with a favourable clinical outcome was still using medication. Jo-1 antibodies predicted the persistent use of medication (OR 4.4, 95% CI 1.3-15.0). We concluded that myositis is associated with a significant disease burden and a high disease-related mortality rate. In the long run, myositis has a major impact on perceived disability and quality of life, even if normal muscle strength has returned. This is of importance if we inform the patients who start treatment about the prognosis.

Chapter 8 contains an overall discussion and offers suggestions for future research.
References