Summary

Pemphigus is a blistering autoimmune disease with autoantibodies against cell junctions between keratinocytes of the epidermis. The introduction, chapter I, describes the state of the art of the pemphigus spectrum. The low annual incidence of approximately 0.3 per 100,000 per year in the Netherlands causes a sparse availability of data in the medical literature, which therefore have to be interpreted carefully. The pemphigus spectrum is subtyped based on 1) clinical presentation and histopathology, 2) subclass of autoantibodies (IgG or IgA), and 3) the targeted autoantigens. The molecular pathomechanism of pemphigus that leads to disrupting of desmosomes between keratinocytes is to a far extend elucidated. The desmosomal complex plays the major role in the cell-cell adhesion of keratinocytes and is targeted by antibodies against desmoglein. Other targets are other non-desmoglein molecular components of the keratinocyte cell membrane. Pemphigus has transformed from an almost invariably fatal disease into one whose mortality is now about 5%. However, morbidity is the main point of attention at the moment, caused by the cumulative dose of long-term used corticosteroids, necessary for sustaining disease control.

In 1997, the PEMPULS trial was designed: an international prospective, multi-centre, double-blind, placebo-controlled parallel-group, randomized clinical trial. The efficacy of adjuvant oral high-dose dexamethasone pulse therapy is studied for the so far hypothesized corticosteroid-sparing effect, and therefore contributes to the effort of adjuvant therapy in general; minimizing the iatrogenic morbidity caused by cumulative corticosteroid dose.

In chapter II, current therapy in pemphigus is discussed. Systemic glucocorticoids still remain for more than 50 years the cornerstone in the treatment of pemphigus. However, they constitute a considerable health risk when used long-term. Therefore a scala of adjuvant therapies are added to the maintenance schedule corticosteroids to minimize these side-effects. No systematic reviews are available in the medical literature.
Summary

to confirm steroid-sparing effects. Choice of treatment, i.e. first and second line immunomodulators, depends on disease phase. Azathioprine is considered to be first choice adjuvant because the low range of side-effects, compared to other immunosuppressive agents, which may have a strong efficacy, but major side-effects.

Chapter III describes pharmacokinetics of oral high-dose dexamethasone. Dexamethasone pulse therapy is mostly given intravenously rather than orally, without evidence to support the necessity of the intravenous route. Oral pulse therapy is preferable, avoiding vena-punctures, decreasing costs, and for patient-convenience. Pharmacokinetics of high-dose oral dexamethasone were determined to develop an oral substitute for intravenous dexamethasone pulse therapy. Bioavailability of high-dose oral dexamethasone is about 60%, and does not differ significantly when 50 mg dexamethasone tablets (58.8%) or 100 mg dexamethasone capsules (63.4%) are administered. Assuming that the effect of megadosis corticosteroid in pulstherapy is determined by the AUC and not by the peak concentration ($C_{\text{max}}$), we may conclude that 300 mg dexamethasone per os in 50 mg tablets can be used as oral substitute for 200 mg intravenous dexamethasone pulse therapy, which is equivalent to 1300 mg prednisolone per os. Clinical effects are studied in the PEMPULS trial, and will be reported in the near future.

Chapter IV describes the effects of dexamethasone pulse therapy in a retrospective study. A total of 207 pulses were administered in 14 pemphigus patients. Side-effects were limited to facial flushing, sleeping disturbances in the first night after administration, and mood changes. There was no difference in these side-effects between oral and intravenous administration. Severe side-effects related to the dexamethasone pulse therapy did not occur. Dexamethasone pulse therapy appeared to be effective to quicken complete remission in 50% of the patients, mainly new pemphigus vulgaris patients. A claim on the hypothesized corticosteroid-sparing effect is not allowed on basis of this retrospective open study.

In chapter V a robust and simple classification into different stages of pemphigus, based on a set of therapeutic benchmarks including a definition of disease activity, is proposed. Monitoring pemphigus is performed by scoring disease activity simply by
counting new pemphigus lesions, and using the Nikolsky sign type I. The proposed staging method was applied a-priori to five newly diagnosed pemphigus patients in the course of their disease. The ELISA titres for desmoglein-1 and -3, as well as the indirect immunofluorescence titres were crosstabulated against the a-priori defined disease stages. ELISA titres of desmogleins seemed to show a good correlation with our proposed staging system, better than the indirect immunofluorescence titres. However, due to the small sample size, we could not perform a statistical test. We conclude that the proposed staging system for disease activity in pemphigus vulgaris is useful for international uniform monitoring pemphigus vulgaris.

In chapter VI monitoring patients on high-dose (2-3 mg/kg/day) azathioprine is explained. Azathioprine has well-documented toxic acute and chronic side-effects. Since the availability of thiopurine methyltransferase (TPMT) enzyme activity test, pancytopenia due to azathioprine, can be predicted and therefore avoided. We reviewed the sequelae of 14 immunobullous patients on high-dose azathioprine and performed both TPMT phenotype (enzyme activity), and TPMT genotype. Assessing the azathioprine metabolism at an individualized level may allow a more accurate and safer choice among the different immunosuppressive modalities. From this study we conclude that high-dose azathioprine (3 mg/kg/day) can safely be used in immunobullous skin conditions.

Chapter VII describes a patient in which a transition of pemphigus vulgaris in pemphigus foliaceus occurred, accompanied by disappearance of antidesmoglein-3 antibodies, and re-occurrence of antidesmoglein-1 antibodies detected by ELISA. This study demonstrates the value of the antidesmoglein ELISA-test in the management of pemphigus.