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Review Article

Therapeutic Apheresis, Immunosuppression, and Human Monoclonal Antibodies in Dermatologic Diseases

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Abbreviations

AAC: Apheresis Committee; ASFA: American Society For Apheresis; BD: Behçet disease; BP: bullous pemphigoid; CTCL: Cutaneus T Cell Lymphoma; DM: Dermatomyositis; ECP: Extracorporeal Photopheresis; HMA: Human Monoclonal antibodies; HPS: Henoch-Schönlein purpura; IF: Immunofluorescence; IgG: Immunoglobulin G; IL: Interleukin; IA: Immunoadsorption; IL: Interleukin; IS: Immunosuppression; IVIG: Intravenous immunoglobin, IMB: Internal Medical Board; PCT: Porphyria Cutanea Tarda, PG: Pyoderma Gangrenosum; PV: Pemphigus Vulgaris, RG: Recommendation Grade; SH: Sulfhydryl; SJS: Steverns-Johson syndrome; SS: Sézary Syndrome; TA: Therapeutic apheresis; TBSA: Total Body Surface Area; TEN: Drug-induced Toxic Epidermal Necrolysis; TNF-α: Tumor Necrosis Factor-α, TPE: Therapeutic Apheresis, TPE: Therapeutic Plasma Exchange; UV: Ultra-Violet

Abstract

Severe and/or refractory dermatological diseases with immunologic origin to conventional therapy have a bad prognosis. Autoimmune blistering diseases have a high morbidity and mortality. Therapeutic apheresis is an essential supportive treatment for severe and refractory dermatological diseases with an immunologic origin, particularly autoimmune blistering diseases. This approach has been shown to significantly improve the prognosis of these diseases. Therapeutic apheresis, combined with immunosuppressive therapy and/or human monoclonal antibodies, has treated successfully autoimmune blistering skin disorders. These diseases are caused by the immune system's targeting of structural proteins in the skin and/or mucous membranes. Improved diagnostic methods have allowed to determine that the incidence and prevalence of these disorders have doubled in the last 15 years to 25 new cases per million people per year owing to an aging population. Over the last 45 years, therapeutic apheresis, in combination with immunosuppression and/or human monoclonal antibodies, has significantly increased survival rates. Therapeutic apheresis using hollow fiber modules is safe and highly effective in eliminating autoantibodies and other toxins from the bloodstream, leading to rapid clinical improvement in dermatological conditions. The guidelines of the for American Application Committee of the American Society for Apheresis are cited dermatologic disorders, which could be treated with therapeutic apheresis

Introduction

Therapeutic apheresis (TA) summarizes all extracorporeal blood purification systems, which removes with special hollow fiber membranes and second hollow fibers, or adsorption technologies with special developed columns [1]. All these extracorporeal techniques allow the elimination of plasma toxins, autoimmune antibodies, or all other pathologic substances. The advantages of these hollow fiber modules since more than 45 years, are a complete separation of cellular components from the plasma. Cell damage as thrombocytes occurs less using membranes than centrifuges for extracorporeal blood separation techniques. During TA with hollow fibers is important too to keep the blood levels of antibodies and/or pathogenic substances on a very low level over a long time during the treatment, in which the pathogenic substances that should be eliminated could enter the intravascular space and could be then removed by the membrane separators [2]. Large numbers of technological, economic, and social factors have an impact on the clinical practice of apheresis [3]. Adsorption technologies with specially developed columns allow a selective separation of toxins, autoantibodies, and other pathological substances from blood without the use of a substitution solution [1].

Therapeutic apheresis procedures are used to remove the plasma together with all high-molecular-weight substances such as immune complexes, antibodies, complement components, cytokines, various toxins, cryoglobulins, and other pathological substances [4]. Only a few prospective controlled trials with sufficient statistical power to draw definitive conclusions about the therapeutic value of TA, are available. However, large numbers of case reports, or small case series of mild to severe dermatological diseases have been reported to improve under treatment with TA.

There are many dermatologic immune-mediated diseases, which represent a heterogeneous group of disorders associated with circulating autoantibodies against various skin and/or mucosal adhesion molecules [5]. The incidence of autoimmune blistering skin diseases has doubled during in the last 10 years in Germany alone, to about 25 new cases per million peoples per year due to improved diagnostic techniques as well as the age of the population [6]. Bullous pemphigoid (BP) is the most common type of subepidermal autoimmune blistering skin disease in Europe, with an incidence of about 13 cases per million people per year [7]. Direct immunofluorescence (IF) microscopy is the diagnostic test for autoimmune blistering skin diseases to demonstrate the presence of tissue-bound autoantibodies and/or of C3 in patient´s skin or mucous membranes. Most dermatologic diseases with immunologic origin require TA, immunosuppression (IS) with steroids, and/

or cytotoxic agents, and human monoclonal antibodies (HMA). The therapy is most individually tailored to the needs of the patient [8,9].

The TA methods which are used in dermatology are therapeutic plasma exchange (TPE), immunoadsorption (IA), Extracorporeal Photopheresis (ECP), adsorptive cytapheresis, lymphocytapheresis [1,8]. In the present review, the authors try to give an overview of the pathogenic aspects indicating that TA, IS, and/or HMAs could be a supportive therapy in severe dermatologic disorders. The Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) is cited for these diseases in which TA is used [8,9].

Dermatologic Diseases

The dermatologic diseases can be classified as intraepidermal blistering pemphigus, such as pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus, and as subepidermal blistering pemphigoid diseases, such as bullous pemphigoid, pemphigoid gestations, and dermatitis herpetiformis [8]. The diagnosis of these dermatologic diseases are done with the direct IF microscopy and the findings of circulating antibodies in the patient's serum. Therapy includes TA, immunosuppressive agents and/or HMAs. However, the treatments used still need to be validated by prospective controlled studies [6].

Pemphigus Vulgaris (PV)

Pemphigus vulgaris is a severe, chronic autoimmune disease of the skin and mucous membranes, and has a poor prognosis. Pemphigus vulgaris is a potentially life-threatening autoimmune disease characterized by acantholytic blisters and erosions and has antibodies against epidermal intercellular substances. Pemphigus vulgaris is a classic example of an autoantibody-induced immune dermatitis which can be recurrent or relapsing [5]. The global incidence of PV ranges from 0.7 to 5 patients per million per year [10]. The average age of onset is the sixth and seventh decade of life, and the patients present with skin lesions that typically that occur typically as flacid blisters. Both genders are equally affected [8]. The blisters can be located on the whole-body surface as well as on the oral mucosa. The deposition of antibodies on the keratinocyte cell surface characterizes PV. The titers of IgG4 antikeratinocyte antibodies can be correlated with disease activity.

The PV can worsen during pregnancy, leading to both maternal and fetal complications. This highlights the importance of effectively managing PV during pregnancy to ensure optimal outcomes for both [11]. Some authors reported severe of PV during and after COVID-19 infection, and after vaccination of COVID-19 [12, 13]. The mRNA vaccines may trigger relapses in patients with autoimmune bullous diseases [14]. The mRNA vaccine upregulates the production of T cell-dependent cytokines such as interleukin (IL) 4, IL-17, and Il-21, interferon γ, and tumor necrosis factor a cytokine, to mediate PV [15]. The development of PV after COVID-19 infection could be triggered by molecular mimicry, bystander activation, epitope spreading, or a combination of autoimmune phenomena. The therapy could be steroids, immunosuppressive drugs, IVIG, and rituximab.

Before the introduction of corticosteroids, PV had a high morbidity and mortality rate. The use of steroids in PV treatment has decreased the mortality rate from 70 % to 100 % to an average of 30 % [8]. However, the long-term use of high doses of corticosteroids may be associated with severe side effects. Further therapeutic options include dapsone, gold, and immunosuppressive agents, such as azathioprine, methotrexate, cyclophosphamide, etc. Other treatment modalities are TPE, ECP, mycophenolate mofetil, chlorambucil, dexamethasone-cyclophosphamide, intravenous immunoglobulins (IVIG), and HMAs such as rituximab [8].

The presence of circulating pathogenic autoantibodies is the rationale for using IA in the treatment of PV. The age groups of 30 – 80 years old, TPE was used to treat PV. The duration of PV prior to the introduction of TPE ranged from 1 month to 25 years. The use of TPE can lead to a reduction of autoantibody levels and subsequent improvement in clinical symptoms. In a large a number of patients, the decline of autoantibody titers, antikeratinocyte cell surface antibodies, and with anti-desmoglein-3 correlated with clinical response [8]. Patients have been successfully treated with TPE, IA and ECP in the treatment of PV [16-19].

Epidermal antibodies, typically belonging to the IgG category, can be easily eliminated with TA [20-22]. The standard therapy of PV is a combination of high-dose glucocorticoids, and immunosuppressive drugs. Additional therapy options include TA, steroid pulse therapy, IVIG, various immunosuppressive drugs (e.g., azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil, and mizoribine), TA and rituximab [23]. In severe cases, a combination of these adjuvant treatments may be used [22].

Therapeutic apheresis has been successfully applied in patients with severe atopic dermatitis and high total serum IgE levels. [24]. Various IA systems and immunosuppressive protocols have been used to reduce the levels of circulating autoantibodies [6]. Immunoadsorption must be combined with an immunosuppressant treatment. Adjuvant IA has a corticosteroid-sparing effect, may lead to earlier remission, and has a lower complication rate and side effects comparable with those of other extracorporeal circulation methods [25, 26]. Levels of autoantibodies have been noted in the reported patients within 1-2 weeks after discontinuation of treatment, which necessitates the continuation of immunosuppression [8]. The AAC of the ASFA has given PV the category III for TPE, IA, and ECP with the recommendation grade (RG) 2B and 2C, respectively (Table 1) [8,9]. The rationale for treatment should include monitoring of autoantibody titers and clinical symptoms. Treatment of ECP should be continued until clinical response is observed [8].

Rituximab, a chimeric murine/human anti-CD20 monoclonal antibody administered in combination with a short course of oral corticosteroids has proven highly effective and generally well-tolerated for moderate and severe PV, and leading to an improvement of the prognosis and higher remission rate [27-29]. Elevated levels of B cell activating factor in the serum may be associated with PV immunopathogenesis, and the rituximab therapy might interfere with B cell repopulation and could be a therapeutic approach in PV [30]. The adverse events of rituximab in the treatment of PV was consistent with that of other treatments for autoimmune disorders. Especially in PV and COVID-19 infection, the evidence for treating PV patients in COVID-19 pandemic is limited, until guidelines for and COVID-19 treatment is available [31]. In addition to TA, immunosuppression, IVIG in the therapy of PV, HMAs, novel therapies such as Bruton kinase and neonatal receptors inhibitors as well as adoptive cellular transfer, may be indicated in severe cases of PV to improve this life-threatening disease [32].

Table 1: Therapeutic apheresis in dermatologic diseases.

Apheresis Application Committee of the American Society For Apheresis [8,9]						
(Category: accepted for TA as first-line therapy; Category II: accepted for TA as second-line therapy; Category III: not accepted for TA, decision should be individualized; Category IV: not accepted for TA, Internal Medical Board (IMB) approval is durable if TA is undertaken [8,9]						
	Category	Recommendation grade	TA modality	Treated volume (TPV)	Replacement solution	Frequency
Intraepidermal blistering PV Pemphigus Vulgaris (PV)	III	2B-2C	TPE, IA, ECP	1-1.5	5% HA, electrol. Solution	Daily or every other day
Subeepidermal blistering BP Bullous pemphigoid	---	---	---	---	---	_____
D-penicillamine-induced pemphigus	---	---	---	---	---	---
Cutaneus T cell Lymphoma - erythrdermic - non-erythrodermic	I III	1B 2C	ECP ECP	1-1.5 1-1.5	---	2 days (one circle)
Dermatitis herpetiformis	---	---	---	---	---	---
Herpes gestations	---	---	---	---	---	---
Progressive scleroderma	III III	2C 2B	TPE ECP	1-1.5 ---	5% HA ---	Daily or every other day
Dermatomyositis	III III	2C 2C	TPE, IA	1-1.5 1-1.5	5% HA ---	
Pyoderma gangrenosum	---	---	---	---	---	---
Epidermal necrolysis (TEN) (Lyell´s syndrome)	III	2B	TPE	1-1.5	5% HA	Daily or every other day
Behcęt disease (BD)	---	---	---	---	---	---
Psoriasis vulgaris	III III IV	2C 2C 2B	TPE, adsorptive Cytapheresis, Lymphocyt Apheresis, ECP	1-1.5	5% HA ---	Daily or every Other day
Henoch-Schönlein purpura (HSP)	III	2C	TPE			
Porphyria cutanea tarda (PCT)	---	---	---	---	---	---

TPV: total plasma volume, TA: therapeutic apheresis, TPE. Therapeutic plasma exchange, IA: immunoadsorption, ECP: extracorporeal photopheresis, 5% HA: 5% human albumin electrolyte solution.

Bullous Pemphigoid (BP)

Bullous pemphigoid is another rare form of subepidermal blistering pemphigus, and frequently. involves a premonitory stage with pruritic urticarial erythema and eczematous lesions followed by the classical bullous stage with tense blisters, erosions and crusts [6]. Bullous pemphigoid is a chronic dermatosis often associated with acute exacerbations, with the formation of bullae blisters usually on the inflamed skin, subepidermal blister formation, and antibodies against the epidermal basal membrane [5]. The consequence is the combined effect of antigen, antibody, complement, and inflammatory cells, whereby lysosomal enzymes actually destroy the basal membrane zone and induce subepidermal blistering [25]. It is unclear if medication or ultraviolet rays can trigger BP. Additionally, the destruction of the basal membrane zone and the release of basal membrane antigens can cause a direct immunological response in predisposed individuals. Bullous pemphigoid may also occur in combination with other autoimmune diseases.

Bullous pemphigoid affects elderly patients in industrialized countries [33,34]. It is often associated with neurological diseases such as dementia, Parkinson's disease, cerebrovascular disease and psychiatric diseases, and some drugs, including loop diuretics and neuroleptics [35]. The association with malignancy or metabolic diseases is still discussed controversially. The therapies of BP are high-dose corticosteroids usually combined with dapsone, doxycycline, methotrexate, or azathioprine [6,36]. The course of BP is not as dramatic as in other forms of the disease. In Europe, the annual incidence of BP is approximately 13-42 new cases per million [37,38]. Some cases of BP have been treated with TA in combination with immunosuppressive drugs, IVIG, and tetracycline [39]. The relevance of autoantibodies in the majority of autoimmune bullous diseases is the rationale to remove the autoantibodies with TA. In particular, IA has been shown to effectively lower antibody levels and leads to a rapid clinical response in patients with autoimmune bullous diseases [40].

Rituximab, a CD20 monoclonal antibody, depletes B lymphocytes and has shown efficacy in severe BP cases [41]. The target interleukin (Il)-4 receptor α, dupilumab, blocks IL-4 and IL-13 and downregulates type 2 helper responses and demonstrated promising results. Omalizumap, an IgE antibody, can reduce disease severity and allows corticosteroids tapering. In some cases with BP. However, a patient with BP who was given dupilumab experienced an unexpected adverse event [42]. Meanwhile, IA and rituximab and especially omalizumab have been established as therapeutic options in the treatment of BP [43,44].

D-Penicillamine-induced pemphigus

D-penicillamine-induced pemphigus is a foliaceus type disease with high lethality and mortality rate that can occur in a long-term penicillamine therapy. It is steroid resistant, and therefore a special indication for TPE [45,46]. The mechanism by which D-penicillamine induces acantholysis of the epidermis has still not been clarified. Immunologic processes similar to those in PV are involved seem to be the origin of these form of pemphigus. The response of the keratinocytes to autoantibody binding via downstream signaling events and eventual keratin filament retraction and apoptosis is the final step in anti-drug-induced acantholysis [46]. Many signaling pathways have been implicated in anti-drug-induced acantholysis, most with circulating autoantibodies against desmoglein 1 [47].

In numerous case reports of drug-induced pemphigus, autoantibodies have been described to have the same antigenic specificity at the molecular level, as autoantibodies from other pemphigus patients [48]. The probability of developing pemphigus after taking penicillamine for at least 6 months is 7 %. Other drugs have been found to induce pemphigus, such as penicillin, ampicillin, rifampicin, pyrazolon derivatives, bucillamine, captopril, combination of aspirin and indomethacin, and combination of propanol and mepbromate [47,49]. Risks for pemphigus are sulfhydryl (SH) group-containing drugs, known as thiol drugs (i.e., captopril) [50]. Drug-induced pemphigus, the drug-triggered pemphigus is considered separate entities [51]. The drug only stimulates a predisposition to develop autoimmune disease in drug-triggered pemphigus, the drug only stimulates a predisposition to develop active autoimmune, disease. Penicillamine and SH group drugs actually induce pemphigus, and other drugs only trigger a previously programmed and ready to go dis immune mechanism [51]. If the offending drug is not stopped immediately, the drug-triggered pemphigus is known to be refractory to all therapy [52].

Some cases of D-penicillamine-induced pemphigus were treated successfully with TA, in combination with an immunosuppressive therapy [53]. The most specific therapeutic option is IA, which depletes only IgG in the patient's plasma with antihuman IgG affinity agarose columns and adsorption of IgG autoantibodies. De novo synthesis of IgG autoantibodies is inhibited by post-apheresis IVIG and/or immunosuppression. The IVIG has also a immunomodulatory effect, so the additional effect of IA is difficult to observe [6]. However, a combination of IA and rituximab showed a rapid and a long-lasting response to concomitant immunosuppression [54].

As an adjuvant drug, rituximab, is indicated in addition to other types of immunosuppressive therapy. However, rituximab may have complications in patients with autoimmune blistering skin disease, including infections, deep venous thrombosis of the lower limbs, pulmonary embolism, long-term hypogammaglobulinemia and neutropenia with an overall mortality of 4 % [54]. The indications, contraindications, and dosage of rituximab treatment for autoimmune blistering skin diseases and the criteria for discontinuing rituximab have been recommended [55].

Cutaneous T cell lymphoma (CTCL)

Cutaneous T-cell lymphoma with its most common types of mycosis fungoides and its leukemic variant, the Sézary syndrome (SS), whose pathogenesis remains elusive and incurable [8]. Therapy is aimed at alleviating symptoms, improving skin manifestations, controlling extracutaneous complications, and minimizing immunosuppressive medications [6]. For refractory disease and aggressive SS, chemotherapy with alemtuzumab and stem cell transplantation is indicated.

Extracorporeal photopheresis is indicated in CTCL, in which circulating malignant CD4+ T cells, ex vivo treatment with 8-methoxypsotalen and UVA light, and reinfused. The therapeutic effect appears to be mediated by in vivo stimulation of antitumor immunity through interactions of irradiated, apoptotic lymphoma cells with antigen-presenting dendritic cells [5,6]. The ECP in combination with non-chemotherapy agents can be considered as a salvage approach for nonresponsive or relapsed patients or those with early-stage disease. The relative lack of immunosuppression and the reduced risk of infection are the advantages of ECP [6]. For a minimum of 6 months, ECP should be planed. It can be reduced to once every 6-12 weeks if maximum response is achieved. If disease progression is observed after 6 months of ECP alone, combination therapy should be considered, and if there is no or minimal response after 3 months of combination therapy, ECP should be discontinued [8]. The AAC of the ASFA has given CTCL erythrodermic the category I and RG 1B and the non-erythrodermic from the category III with RG 2C for ECP (Table 1) [8,9]. The Therapy is stage-adapted with skin therapies such as UV-light and corticosteroids and systemic therapies such as retinoids, interferon, chemotherapy, HMAs, and/or radiation therapy in advanced stages [56,57]. In severe cases and highly-selected patients, allogenic stem-cell transplantation can provide long-term overall survival [58,59]. Other new therapy strategies may include more immunomodulatory agents, vaccines and HMAs [60].

In dermatitis herpetiformis and herpes gestations TPE is, in combination with a immunosuppression probably successful due to the pathogenesis of severe cases [5,61]. Herpes gestations or pemphigoid gestations is an autoimmune blistering disease that occurs in women during the second or third trimesters of pregnancy or even puerperium. The disease is rare, and the incidence of which has been approximately one case in every 40,000-60,000 pregnancies [61]. Resistant to corticosteroids, other treatments have been indicated including immunosuppressive agents, such as cyclosporin, azathioprine, tacrolimus, tacrolimus, and TPE. Dermatitis herpetiformis produces anti-desmoglein-3 autoantibodies and may be a variant of PV with unique clinical and histological features [62].

Progressive scleroderma, systemic sclerosis

Systemic scleroderma or systemic sclerosis, also known as progressive scleroderma, is a rare, generalized autoimmune disorder, which is characterized by vascular abnormalities, fibrosis, inflammatory changes, and late-stage atrophy/obliterative vasculopathy. Localized scleroderma forms, have a longitudinal or circumscribed skin involvement [63,64]. Systemic sclerosis, is an autoimmune-mediated inflammatory disease, leads to pulmonary fibrosis or to scleroderma renal crisis, which is a life-threatening complication with a mortality rate of 20 % [65,66].

The therapy for interstitial lung disease/pulmonary fibrosis for induction, is intravenous cyclophosphamide and mycophenolate mofetil or azathioprine and/or rituximab [67]. The first-line therapy for scleroderma renal crisis is an angiotensin-converting enzyme inhibitor and/or a angiotensin receptor blocker. Particular, HMAs, such as rituximab, tocilizumab, etc., have been associated with significant improvements in systemic sclerosis [68]. The efficacy of TA and/or ECP as a long-term treatment in progressive scleroderma is still disputed (Table 1) [5,69].

Dermatomyositis (DM)

Dermatomyositis is also a rare heterogenous systemic autoimmune disease with multiple organ involvement that can result in significant disability and mortality. Dermatomyositis is an idiopathic inflammatory myopathy that most severity is manifests with proximal muscle weakness, which is associated with extra-muscular pathology including characteristic skin lesions and with involvement of the lung, gastrointestinal, joint, and cardiac [69,70]. Disease based on the presence of systemic symptoms, and myositis-specific antibodies [71].

In addition to corticosteroids, there are steroid-sparing immunosuppressive drugs including methotrexate, azathioprine, calcineurin inhibitors, mycophenolate mofetil, and cyclophosphamide [72]. Rituximab has been shown to improve refractory DM [73]. The combination of mycophenolate mofetil, rituximab and TPE or IA with polymyxin B columns is indicated in antibody-positive DM. However, the use of TA in DM is still controversial. Especially in severe DM with anti-melanoma differentiation-associated gene 5 antibody is TA indicated to control disease activity [74,75]. In addition to TPE, IA with polymyxin B immobilized fiber columns have been found to be very effective [74]. The AAC of the ASFA has given DM the category III with RG 2C (Table 1) [5,9,76]. Further clinical studies are necessary to determine the optimal therapy strategy for DM.

Pyoderma gangrenosum (PG)

Pyoderma gangrenosum is also a rare, polyetiological syndrome caused by a pathological immune reaction. The disease occurs together with colitis ulcerosa in more than 40% of the cases. Vasculitis lesions in the vessel walls, have been found to contain granular deposits of IgG, C3, complement, and IgM [77]. Pyoderma gangrenosum, a non-infectious neutrophilic dermatosis, starts with sterile pustules that rapidly progress to painful ulcers of variable depth and a size, and underdetermined violaceous borders [5]. With an underlying disease is PG associated in 17 – 74% most commonly inflammatory bowel disease colitis ulcerosa, rheumatological and hematological diseases, and malignancy. Pyoderma gangrenosum pathogenesis is complex, and is clinically characterized by painful, rapidly evolving cutaneous ulcers with undermined, irregular, erythematous-violaceous edges [78].

The diagnosis of PG is based on the history of the underlying disease, typical clinical presentation and histopathology, and exclusion of other disorders that could lead to a similar presentation [79]. Clinical aspects include ulcerative or classic, pustular, bullous or typical, vegetative, peristomal signs. Subcorneal pustular dermatosis is an uncommon relapsing symmetric pustular eruption that involves flexural and intertriginous areas. This disease can be either idiopathic or associated with cancer, infections, medications, or systemic disorders [80]. Prospective randomized controlled studies are currently unavailable due to the low incidence of pyoderma gangrenosum. However, studies with a limited number of cases have been published [80,81].

Corticosteroids and cyclosporin are the first line treatment for PG. In refractory cases, additional treatments such as mycophenolate mofetil, tacrolimus, TNFα inhibitors infliximab, adalimumab, and others, and/or TA are indicated [81]. Other potential treatment options include IVIG, TNFα inhibitors, and IL-1 receptor antagonists [82,83]. The adsorptive granulocyte/monocyte apheresis has been successfully used once or twice a week in patients with PG. This method is useful and a safe treatment modality for PG [84]. Recent advances in therapy the prognosis of PG remains unpredictable.

Drug-induced toxic epidermal necrolysis (TEN), Lyell´s syndrome

Lyell´s syndrome is a life-threatening drug reaction characterized by extensive destruction of the epidermis and mucosal epithelia. The eyes are typically involved, and with a high mortality rate [5]. Lyell´s syndrome and the Steven-Johnson syndrome (SJS) are closely related, they differ in severity and outcome. The TEN and the SJS are rare diseases that present severe skin manifestations. The incidence is one to three cases per million people per year in Europe and the United States [85]. In about 80% of TEN patients, different drugs are most commonly implicated. These diseases have high mortality rates. Notably, TEN is the most severe form of drug-induced skin reaction, and is defined as epidermal detachment of 30 % of total body surface area (TBSA). An epidermal detachment of 10 %. TBSA presents SJS, whereas involvement of 10-30 % of TSBA is defined as SJS/Ten overlap [86]. To distinguish TEN from severe forms of erythema multiforme, there are helpful, etiological, clinical and histological characteristics. The patho-mechanism suggests that keratinocytes of both are the cytokines. Tumor necrosis factor-α and oxidative stress induce a combination of apoptotic and necrotic events [87].

Therapeutic plasma exchange is a highly effective treatment for the acute phase of toxic epidermal necrolysis. The allergic or toxin-induced is usually triggered by drugs acting like hapten [88]. Sulfonamides, β-lactam, tetracyclines, quinolones, phenytoin, phenobarbital, carbamazepine, antiretroviral drugs, nonsteroidal anti-inflammatory drugs, and allopurinol are the drugs most commonly associated with this form [89]. Early administration of TPE is recommended for Lyell´s syndrome, a rare but potentially fatal condition with a mortality of approximately 50 %. Therapeutic plasma exchange is safe and may reduce the mortality in severely ill TEN patients [90]. The combination of TPE and IVIG has been also shown to improve outcomes in severe TEN [91,92]. The AAC of the ASFA has given the TEN for TPE the category III and the RG 2B (Table 1) [8,9]. In patients with TEN, infliximab, a monoclonal antibody to TNF-α, has been successfully applied, and appears to improve outcomes [89]. However further studies are necessary to define the most successful therapy for TEN.

Behçet´s Disease (BD)

Behçet´s disease is a multisystemic inflammatory disorder and presents with the involvement of mucocutaneous ocular, vascular, central nervous and gastrointestinal systems. This disorder is an idiopathic, chronic, and recurrent disease characterized by exacerbation alternating with plasma quiescence, episodic pan-uveitis, and aggressive non-granulomatous occlusive vasculitis of the arteries and veins of any size with explosive ocular inflammatory attacks that primarily affect the retinal and anterior segment vasculature of the eyes (93). Necrotizing vasculitis is the most common cause of central nervous system involvement in this disease, often leading to death. In these patients' ocular manifestations occur in 70-85%, with occlusive vasculitis being the underlying mechanism in all organ systems [5].

Behçet´s disease is usually diagnosed in both genders during the third or fourth decade of life. It is much more prevalent in populations along the ancient "Silk Road", extending from Eastern Asia to countries in the Middle East and the Mediterranean, compared to Western countries [94]. Ethnic diversity may also influence the severity of progression and clinical manifestations [95]. Important genetic factors of BD pathogenesis, and HLA-B51 antigen is the strongest genetic susceptibility factor [94]. Behçet´s disease has a high mortality rate, especially in young male patients. The most significant causes of death.is the large-vessel, neurological, gastrointestinal system, and cardiac involvement.

The effect of TPE in BD, with a debated immune-pathogenesis, is not clear. Therapeutic plasma exchange has shown success in individual cases [96]. Selective adsorption apheresis, granulocytapheresis might be effective and safe in patients with severe BD [97]. Further therapies such as cyclosporin A, tacrolimus, and TNF-blocking agents like infliximab, etanercept or adalimumab have also been reported as successful and safe treatments for severe BD [97,98]. Besides the TNF-inhibitors IL-1 such as utstekinumab, secukinumab, or tocilizumab are indicated in refractory BD in addition to TNF inhibitors [99].

Psoriasis vulgaris

Psoriasis vulgaris is a common autoimmune chronic inflammatory skin disease which affects approximately 2 % of the world´s population. The immunopathogenic mechanism is the secretion of type 1 (Th 1) cytokines by T cells and their activation [100]. Cytokines, which are intercellular molecules, play an important role in the development and maintenance of cutaneous inflammation have the cytokines, which are intercellular molecules [101]. The pathogenesis of psoriasis vulgaris is still for the most part unclear: Autoantibodies, circulating immune complexes, and cytokines are thought to be responsible for triggering flares of the disease or a new attack [5]. However, there has been no correlation between the levels of circulating immune complexes, disease activity, or response to treatment. Psoriasis vulgaris, as a chronic inflammatory disorder, is associated with impaired skin barrier function, and show elevated IgE levels in a significant proportion of patients with this disease, but its elevated levels were not associated with treatment outcome [102].

The indication for TPE is based on the presumption of immunopathogenesis. However, TPE may be beneficial in patients with psoriatic arthropathy who do not respond to conventional therapy [103]. Other methods are ECP, adsorptive cytapheresis, and lymphocytapheresis, which has been categorized as III by the AAC of the ASFA with the RG 2C. The skin lesions did not respond to ECP, therefore ECP has the category IV and the RG 2B (Table 1) [100,103,104].

Besides the treatment with calcipotriol and betamethasone valerate, biologic, the choice of biologic treatment in psoriasis vulgaris show to be more helpful [105]. These treatments include blocking TNF-α factors such as infliximab, oretanercept, JAK inhibitors such as tofacitinib and interleukin-17A inhibitors such as secukinumab and others. All biologic agents are safe and effective in treating psoriasis vulgaris [106-108]. However, further investigations are needed to determine the long-term effectiveness of these treatments.

Henoch-Schönlein purpura (HSP)

Henoch-Schönlein purpura is a systemic vasculitis that affects small vessels. The disease typically affects the lower limbs, and is often associated, with varying degrees, of joints, gastrointestinal and renal involvement [5]. Henoch-Schönlein purpura is a systemic disease where antigen-antibody (IgA) complexes that activate the alternative complement pathway, leading to inflammation and small-vessel vasculitis [109].

The presence of two or more of the following criteria defines HSP: age of disease onset, mostly 20 years or younger, palpable purpura, acute abdominal pain, and granulocytic infiltration in the walls of arterioles or venules [110]. Henoch-Schonlein purpura is characterized by small-vessel vasculitis with predominant IgA vascular deposits, and all patients develop palpable purpura. Subepidermal hemorrhage and small-vessel necrotizing vasculitis lead to the purpura [8]. IgG autoantibodies directed at mesangial antigens may play a role in the pathogenesis. Necrotizing vasculitis leads to organ dysfunction or hemorrhage in other organs. However, the precise role of IgA or antibodies in the disorder's pathogenesis remains unclear. According to various investigations, anti-glycan antibodies recognize galactose-deficient IgA1 leading to the formation of circulating immune complexes and the mesangial deposition, which is turn causes renal injury [111].

Patients with IgA nephropathy, including HSP nephritis, who present a rapidly progressive glomerulonephritis have a poor prognosis despite aggressive immunosuppressive therapy [112]. Therefore, TPE is indicated as an adjunctive therapy with immunosuppression. In the AAC of the ASFA, TPE has category III with RG 2C for the crescentic form and severe extra-renal manifestations of HSP (Table 1) [8,9]. Other therapeutic strategies for severe HSP, besides corticosteroids, are methotrexate,

cyclophosphamide, or azathioprine. Further therapies are mycophenolate mofetil, or cyclosporine A, or tacrolimus, are all safe and effective [113]. Although rituximab and dapsone have been successful, there is still a lack of prospective randomized clinical studies proving treatment efficacy [114]. It is difficult to establish treatment protocols due to spontaneous recovery even in patients with severe clinical and histological presentation and of late evolution to chronic kidney disease in patients with mild initial symptoms [115].

Porphyria Cutanea Tarda (PCT)

Porphyria cutanea tarda is a metabolic disease of hem biosynthesis caused by decreased activity of uroporphyrinogen decarboxylase. It is characterized by fragility, erosions, bullae, milia, and scars on sun-exposed skin [116]. Excess porphyrins in the skin interact with light of approximately 400-nm-wave length radiant energy interact with excess porphyrins in the skin, forming reactive oxygen species. The disease can be familial, acquired, or toxic. Alcohol, estrogen, iron, polyhalogenated compounds can induce clinical expression of PCT in susceptible individuals. PCT is also associated with an increased incidence of the hemochromatosis gene [116].

Porphyria cutanea tarda is the most common form of human porphyria, due to hepatic deficiency of uroporphyrinogen decarboxylase, which is acquired in the presence of iron overload and other factors [117]. The pathogenesis is the identification of the iron overloaded-induced inhibitor of hepatic uroporphyrin decarboxylase activity that causes the PCT, and the identification of an X-linked form of erythropoietic porphyria due to gain-of-function mutations in erythroid-specific 5-aminolevulinate synthase [118]. During hematopoiesis, protoporphyrin accumulates in the maturing red blood cells. Free protoporphyrin diffuses across the red blood cell membranes and binds to plasma proteins, when red blood cells enter the circulation. The liver extracts protoporphyrin from the plasma, most of which is excreted unchanged into the bile, with the remainder being metabolized to hem. Some protoporphyrin some protoporphyrin is subsequently reabsorbed during enterohepatic circulation [119]. Besides phlebotomy, TPE as a treatment for PCT is reported by many authors [5,120].

Summary

Other dermatological diseases, such as necrotic xanthogranuloma or scleromyxedema, are not mentioned here, due to the oncological treatment or the lack of clinical data. Patients with neurodermatitis, alopecia, totalis, and other dermatological diseases were successfully treated with the double filtration plasmapheresis system with a special double filter TKM 58 [121,122] The mentioned TA methods are still technically complicated and expensive.

Physicians are committed to helping all patients entrusted to them, and this means providing medical treatment – including apheresis techniques. This demand presents a great challenge to physicians, politicians, health organizations, and especially manufactures. Medical supply companies constantly justifies the high costs due to the expensive research and development required. All those involved in the healthcare system must strengthen their cooperation in the respect. Pemphigus vulgaris is an example of antibody-induced immune dermatosis. In patients with severe symptoms who either received high doses of conventional agents and/or have an aggressive and rapidly progressive disorder, TPE, or IA and ECP are indicated. Bullous pemphigoid is a rare form of subepidermal blistering pemphigus, and is not as dramatic as other autoimmune diseases and responds well to conventional therapy. In cases of severe BP and d-penicillamine-induced pemphigus, TPE or IA in combination with immunosuppression are recommended [5].

Chemotherapy and stem cell transplantation are indicated for more aggressive forms of CTCL The AAC of the ASFA has given CTCL the category I and the RG 1B for ECP. ECP has the advantage of causing less immune suspension and a lower risk of infections. Therapeutic plasma exchange or intravenous immunoglobulin administration can be successful in severe cases of progressive scleroderma, dermatomyositis, TEN, psoriasis vulgaris, and HST. The first-line therapy for these diseases is immunosuppression. Biologics, or TA could act as second-line therapy. In cases of Behçet´s disease, dermatitis herpetiformis, herpes gestations, and pyoderma gangrenosum, TA may be used as a second-line therapy. The last four mentioned diseases are not discussed in the guidelines of the AAC of the ASFA.

A well-trained and experienced physician can overcome technical difficulties to complete the procedure without complications [123]. However, for all mentioned diseases the quotient relevant for cost-effectiveness assessment (cost of treatment – cost saved: improvement in life quality) must be discussed and calculated precisely by all involved parties [124]. Every effort should be made to delay the progression of acute and chronic diseases. Therapeutic apheresis is clearly an important tool in the treatment of many complex conditions both currently and in the future [125]. In most patients the treatment with TA must be combined with a immunosuppression, IVIG, and/or biologic agents.

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