

Therapeutic Apheresis and/or Monoclonal Antibodies in Dermatological Diseases

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Abstract

Therapeutic Apheresis (TA) is increasingly applied as support treatment in dermatological diseases especially in severe and/or refractory autoimmune bullous diseases. Since the pathogenetic relevance of autoantibodies could be defined in various diseases, disease-specific adsorbers have been developed. Especially, dermatologic immune-mediated diseases respond to TA. The different TA methods, such as Therapeutic Plasma Exchange (TPE), Immunoabsorption (IA), adsorptive cytopheresis, Extracorporeal Photopheresis (ECP) were discussed elsewhere [1,2]. Dermatologic immune-mediated diseases represent a heterogeneous group of disorders associated with circulating autoantibodies against distinct adhesion molecules of the skin and/or mucosa. The incidence of autoimmune blistering skin diseases for example in Germany has doubled during in the last 10 years, to about 25 new cases per million humans per year, because of improved diagnostic techniques as well as the age of the population [3]. The incidence of Pemphigus Vulgaris (PV) in Europe is one to two cases per million humans per year, and 80% of pemphigus patients have PV [4]. Bulbous Pemphigoid (BP) is the most common type of subepidermal autoimmune blistering skin disease in Europe, with an incidence of about 13 cases per million humans per year.

Introduction

Pemphigus vulgaris (PV) is a severe, chronic disease of the skin and mucous membranes, has poor prognosis and acantholytic blisters and erosion, and is characterized by the presence of antibodies against epidermal intercellular substances [5]. Both genders are equally affected with the mean age of onset in the sixth and seventh decade of life, and the patients present with skin lesions that occur typically as flaccid blisters [2]. The blisters can be located on the entire body surface as well as on the mucous membranes of the mouth. PV has a high morbidity and mortality before the introduction of corticosteroids. They reduced the mortality rate from 70% to 100% to a mean of 30% [2]. The conservative therapy include high doses of corticosteroids, dapsone, gold, and systemic antibodies alone or in combination with other immunosuppressant agents in usually dosages, such as azathioprine, methotrexate, and cyclophosphamide. Newer therapeutic modalities are mycophenolate mofetil, chlorambucil, dexamethasone-cyclophosphamide, IVIG therapy, TPE, ECP and rituximab [2]. The rationale for using TPE in the treatment of PV based on the presence of circulating pathogenic autoantibodies. The frequency of TPE and IA is 3 to 6 Treatments in two weeks, and then after the titer of the antibodies in the blood. For ECP, the frequency is 3 to 4 treatments in one week, and then after the antibody titers. The treated volume is for all diseases 1 to 1.5 total plasma volume. The substitution solution TPE is usually a 5% human albumin-electrolyte solution or a part of fresh frozen plasma for all diseases. The goal of TPE is to reduce the level of autoantibodies with subsequent improvement in clinical symptoms. The decline



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in autoantibody titers, antikeratinocyte cell surface antibodies, and anti-desmoglein-3 correlated with clinical response in a number of patients [2,6-9]. The antiepidermal antibodies, which usually belong to the IgG category, can be easily eliminated with TPE [6,7].

Bullous pemphigoid (BP) is another form of subepidermal blistering pemphigus; BP is rare. BP frequently involves a premonitory stage with pruritic urticarial erythema and eczematous lesions followed by the classical bullous stage with tense blisters, erosions, and crusts [8]. BP 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. Thus, BP can also occur in combination with other autoimmune disorders. The course of this pemphigus disorder is not as dramatic as other forms of the disease, with good response to high-potency corticosteroids, which are usually combined with dapsone, doxycycline, methotrexate, or azathioprine in usually dosages [3]. BP has an annual incidence of about 13-42 new cases per 1 million in central Europe and the United Kingdom [9,10]. Only a few cases have been treated with TPE up to now [11]. After 3 to 5 treatments in one week, we could see if TPE or IA can decrease the antibody titer. In very low antibody titers, the frequency of the treatments can decrease, too. Because the pathogenic relevance of autoantibodies was clearly demonstrated in the majority of autoimmune bullous diseases, removal of autoantibodies, therefore, TPE is indicated. IA and rituximab have been established additional therapeutic options [12].

D-Penicillamine induced pemphigus, steroid-resistant pemphigus, is a foliaceustype disease with high lethality and mortality rate, which can occur as a side effect in long-term penicillamine therapy, which is a particular indication for TPE [13]. Only case reports of D-penicillamine-induced pemphigus treated successfully with TA were reported in combination with immunosuppression. IA is the most specific therapeutic option, in which only the pathogenic IgG is depleted in the patient's plasma. Three to 5 treatments of TPE or IA and immunosuppressive drugs in one or two weeks are necessary to an improvement of the disease. A combination of IA and rituximab showed rapid and long-lasting response of concomitant im-

munosuppressive medication [14]. Rituximab, in usually dosages, is almost given as an adjuvant drug, i.e., in addition to another type of immunosuppressive treatment. Complications of rituximab in patients with autoimmune blistering skin diseases include infections, deep venous thrombosis of the lower limbs, pulmonary embolism, longterm hypogammaglobulinemia, and neutropenia with an overall mortality of 4%.

Mycosis fungoides and its leukemic variant, Sézary syndrome (SS), are the most common types of Cutaneous T-Cell Lymphoma (CTCL) whose pathogenesis remains elusive [2]. CTCL is incurable. Therapy is aimed at alleviating symptoms, improving skin manifestations, controlling extra cutaneous complications, and minimizing immunosuppression [8]. Chemotherapy is recommended for aggressive SS, with alemtuzumab in usually dosages and stem cell transplantation being considered for refractory disease. In CTCL ECP is indicated. ECP involves the collection of circulating malignant CD4+ T cells, ex vivo treatment with 8-methoxypsoralen and UVA light and reinfusion of the cells. The therapeutic effect appears to be mediated by *in vivo* stimulation of antitumor immunity through the interactions of irradiated, apoptotic lymphoma cells with antigen-presenting dendritic cells [2]. ECP should be planned for a minimum of 6 months (2 to 3 treatments per week in the acute phase), or it can be reduced to once every 6-12 weeks.

TPE is in combination with immunosuppression probably successful due to the pathogenesis of severe cases of dermatitis herpetiformis and herpes gestationis [15,16]. Herpes gestationis or pemphigoid gestationis is an autoimmune subepidermal blistering disease that occurs in women in the second or third trimesters of pregnancy or even puerperium. It is a rare skin disease, the incidence of which has been estimated of approximately one case in every 40,000–60,000 pregnancies [16].

Scleroderma or systemic sclerosis is a rare, generalized autoimmune disease. Scleroderma is characterized by vascular abnormalities, fibrosis, inflammatory changes, and late-stage atrophy/obliterative vasculopathy. Localized scleroderma forms show a longitudinal or circumscribed skin involvement [17]. The effectiveness of TPE in progressive scleroderma and dermatomyositis is still disputed.

Pyoderma gangrenosum (PG) is a rare, polyetiological syndrome based on a pathological immune reaction. In over 40% of cases, this disease occurs together with colitis ulcerosa. In the vessel walls of vasculitic lesions, granular IgG, C3, complement, and IgM deposits have been observed [18]. PG is a non-infectious neutrophilic dermatosis that usually starts with sterile pustules that rapidly progress to painful ulcers of variable depth and size with undermined violaceous borders. In 17%-74% of cases, PG is associated with an underlying disease, most commonly inflammatory bowel disease, rheumatological or hematological disease, or malignancy. PG is characterized by painful, enlarging necrotic ulcers with bluish undermined borders surrounded by an advancing zone of erythema; its clinical variants include ulcerative or classic, pustular, bullous or typical, vegetative, peristomal, and drug-induced. It can be idiopathic or associated with cancer, infections, medications, and systemic diseases [19]. The treatment with corticosteroids and cyclosporin is documented as first-line therapy. In cases that do not respond

to this treatment, alternative therapeutic procedures (e.g., systemic corticosteroids and mycophenolate mofetil; mycophenolate mofetil and cyclosporin; tacrolimus; infliximab in usually dosages, or TPE (8 to 10 treatments) are recommended [20].

Drug-induced Epidermal toxic necrolysis (TEN), also known as Lyell's syndrome, is a life-threatening drug reaction characterized by extensive destruction of the epidermis and mucosal epithelia. The eyes are typically involved in TEN. The disease has a high mortality rate. TEN and the Stevens-Johnson Syndrome (SJS) are closely related, although their severity and outcome are different. The SJS and TEN are rare but present severe skin manifestation. They are estimated to occur in one to three people per million per year in Europe and the United States [21]. They are characterized by a low incidence but high mortality, and drugs are most commonly implicated in 80% of TEN cases. TEN is the most severe form of drug induced skin reaction and is defined as epidermal detachment of 30% of total body surface area [22]. In Lyell's syndrome, the acute phase can be very successfully treated by TPE. The allergic or toxin-induced skin necrolysis is usually triggered by a drug acting like a hapten [23]. Lyell's syndrome is fortunately very rare but has a high mortality rate, approximately 50%, and thus, early administration of TPE is justified, 6 to (8 to 10 treatments) every day or every other day. TPE is a safe intervention in severely ill TEN patients and may reduce the mortality in this severe disease [24].

Behcet disease a multisystem inflammatory disorder, presents with the involvement of muco-cutaneous, ocular, vascular, central nervous and gastrointestinal systems. It is an idiopathic, chronic, and recurrent disease characterized by exacerbation alternating with plasma of 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 eye [25]. Central nervous system involvement, most often due to necrotizing vasculitis, may be the most protean manifestation of the disease, leading to death. The frequency of ocular manifestations is 70%-85% in these patients.

Although TPE has been has been successful in individual cases [26]. The frequency is 3 to 6 treatments daily or every other day, a chronic treatment of TPE with 1 treatment every two or four weeks for two or three months is possible, too. In recent years, there have been reports on the successful treatment with implementation of cyclosporin A, tacrolimus, or infliximab, etc.

Psoriasis vulgaris is a common autoimmune chronic inflammatory skin disease that affects approximately 2% of the world's population. Fundamental for its immunopathogenic mechanism is the secretion of type 1 (Th 1) cytokines by T cells and their activation [27]. TPE may be beneficial in patients with psoriatic arthropathy and not responding to conventional therapy [28]. However, blocking TNF- α by infliximab or etanercept has shown particular promise, especially in the management of psoriasis.

Henoch-Schönlein purpura (HSP) is a systemic vasculitis that affects vessels of small size. The vascular purpura is usually confined to the lower limbs and is associated, at varying degrees, with joint, gastrointestinal, and renal involvement. It is a systemic disease

where antigen-antibody (IgA) complexes activate the alternate complement pathway, resulting in inflammation and small-vessel vasculitis [29]. HSP is defined as the presence of two or more of the following criteria: age of disease onset (20 years or younger), palpable purpura, acute abdominal pain, and granulocytic infiltration in the walls of arterioles or venuoles. All patients develop palpable purpura. In the skin, these deposits lead to subepidermal hemorrhage and small-vessel necrotizing vasculitis producing the purpura (2). IgG autoantibodies directed at mesangial antigens may play a role in pathogenesis. In other organs, necrotizing vasculitis leads to organ dysfunction or hemorrhage. The recommendation for TPE are severe cases. Eight to 10 treatments daily or every other day until the antibodies disappeared.

Porphyria cutanea tarda (PCT), a genetic enzyme defect, was also considered as being a treatable condition with possible indication for TPE (1). PCT is a metabolic disorder of the hem biosynthesis caused by decreased activity of uroporphyrinogen decarboxylase [30]. PCT is manifest by fragility, erosions, bullae, milia, and scars on sun-exposed skin. Excess porphyrins in the skin interact with light of approximately 400-nm-wave length radiant energy, forming reactive oxygen species. PCT is categorized as familial, acquired, or toxic. Factors that may induce clinical expression of PCT in susceptible individuals include alcohol, estrogen, iron, polyhalogenated compounds, and viral infections. Many authors report TPE as a treatment for PCT. After three treatments in one week, one treatment every weeks or every other week is usually, however, it depends of the clinical symptoms. Nevertheless, no controlled studies are available.

Other dermatological diseases, such as necrotic xanthogranuloma and scleromyxedema, are not mentioned due to the oncological treatment or the lack of clinical data. All mentioned TA methods are still technically complicated and very expensive. The costs of the mentioned TA methods vary widely in Germany; for example, for TEP are between 830 and 1,620€, for IA between 2,040 and 2,240€, and for ECP between 1,600 and 2,700€ per treatment [14]. It is the responsibility of the manufacturers to develop simpler and less costly techniques.

Conclusion

TA has been successfully used in various antibody-mediated diseases. PV is a classic example of antibody-induced immune dermatosis. TPE or IA and ECP are indicated in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease. BP is another rare form of subepidermal blistering pemphigus. BP is not as dramatic as other autoimmune diseases with good response of conventional therapy. TPE and IA in combination with immunosuppression are indicated in BP and d-penicillamine-induced pemphigus only in severe cases. Chemotherapy and stem cell transplantation are indicated for more aggressive forms of CTCL. The advantage of ECP is the relative lack of immune suspension and reduced risk infection. In severe cases of progressive scleroderma, dermatomyositis, TEN, psoriasis vulgaris, and HST, TPE or IA can be successful. In these diseases, which do not respond to this therapy, the first-line therapy is immunosuppression in usually dosages. Other immuno-suppressants, biologics, or TA could act as second-line therapy. TA is only indicated in severe cases of Behçet disease, PG, dermatitis herpetiformis, and herpes gestationis

as second-line therapy. However for all mentioned diseases, the quotient relevant for cost-effectivity assessment [cost of treatment-cost saved]: [improvement in life quality] must be discussed and calculated exactly by all the persons involved.

Physicians are committed to helping all patients entrusted to them to the best of their knowledge, and this means that medical treatment – and particularly the apheresis processes – must become affordable. This demand represents a great challenge to physicians, politicians, health organizations, and above all to the manufacturers. Industry constantly justifies the high costs with the extensive research and development required. All those involved in the health-care system must intensify their cooperation in this respect.

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