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RESEARCH ARTICLE

Auto-Immune Disorders treated with Therapeutic Apheresis

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ABSTRACT

Auto-immune diseases based on an immune pathogenesis produce auto antibodies and circulating immune complexes, which cause inflammation in the tissues of various organs. In most cases, these diseases have a bad prognosis without treatment. Therapeutic plasma exchange with hollow fiber modules is used since more than 40 years and has led in combination with immunosuppressive therapies to a steady increase in survival rates over the last decades. Here we provide an overview of the most important pathogenic aspects indicating that therapeutic apheresis can be a supportive therapy in auto immune diseases, such as renal, neurologic, hematologic and dermatologic diseases.

Introduction

The term auto immune disease relates to diseases caused by antibodies acting against the body´s own tissue. The term describe in more than 80 types of illness, the common characteristics of which is immune-mediated destruction of intracellular structures in connective tissue, resulting in fibrinoid tissue damage [1]. Autoimmune diseases, with the exception of rheumatoid arthritis and autoimmune thyroiditis, are individually rare, but together affect approximately 5% of the population in western countries. They are poorly understood group of diseases [2]. Viral infections and other influences can lead to altered native antigen with a loss of suppression [1]. Typically, antinuclear antibodies are to be found against most nuclear structures. Vasculitis is common to all these diseases, and is most easily demonstrated histological in the precapillary arterioles and post-capillary venuoles. The same chronic cellular infiltrate are seen in immune-mediated synovitis, with its clinical manifestations of arthralgia or arthritis.

The cause of auto immune reactions is still generally unknown. The spectrum of auto immune diseases ranges from those diseases in which autoimmunization are solely responsible for the disease condition, to those in which it possibly has a major influence on the further course of the diseases, and those in which the auto immunization phenomena are probably only of diagnostic impotance [2], These auto antibodies can also be directed at all blood cells [3].

Inflammation is a complex set of events accompanied by the release of many different soluble substances, such as antibodies that diffuse away from the site of their production. Auto antibodies are not necessarily primarily auto aggressive or destructive. They only lead to inflammatory tissue reaction when, through their binding to cells and through complement activation, the reaction chain of the serum complement system is triggered.

Immune Complex (IC) is a physiological process and serves to eliminate foreign material, such as bacteria, their components and viruses. If such ICs are formed, they are removed from the blood by the adhesion of the Fc-fragments of the antibodies to the corresponding phagocyte receptors in the liver and spleen. ICs are deposited preferentially in certain sites throughout the body, the kidneys, the joints, the lungs and the skin. The kidney accumulates ICs because the blood pressure in the glomerular capillaries is four times higher than in other capillaries and because the glomerulus retains immune ICs by a simple filtering effect. Similarly, ICs may also accumulate in other body filters. CICs are involved in the regulation of various immune phenomena It is possible to interrupt the pathological process by eliminating antibodies by Therapeutic Apheresis (TA). The methods of TA, which are available and mentioned here, were discussed in detail by Bambauer et al [3-5].

Methods

The introduction of hollow fiber modules in TA shows a complete separation of the corpuscular components from the plasma and due to increased blood flow rate and higher efficacy [3,4]. It is no advantage that TA using centrifuges has shorter treatment times such as TA using hollow fibers shown by Hafer et al [6]. More important is to keep the blood levels with antibodies and/other pathogenic substances on a very low level over longer time during the treatment. In this situation the substances that should be eliminated could invade into the intravascular space and be eliminated by the membrane separators.

The conventional TPE equipments are, however, not perfect, because the filtered plasma fractions have to be discarded. Substitution solutions supplemented with human albumin, plasma substitutes (e.g., gelatine solutions), or fresh frozen plasma are used to replace the discarded fractions [3].

Cascade Filtration (CF), or double filtration plasmapheresis seems to be superior to conventional plasmapheresis but less effective than adsorption or precipitation techniques [7]. The secondary membrane in CF has a cut off of approximately one million or less Daltons. Clinically satisfactory separation is currently possible for albumin (MW approximately 65,000 daltons) and macromolecular substances of 500,000 daltons. Separation of albumin and IgG (MW 160,000 daltons) cannot be exactly performed with the membranes currently available, and due to the molecular structure of immunoglobulins will probably not be entirely possible with secondary membranes, either [4].

1. Protein-A immunoadsorption (IA):

Protein-A was found to bind more than immunoglobulin or Fc-fragment, demonstrating that protein-A contains two or more identical or similar structures [8]. Protein-A has also various structural elements for linking to the cell wall. Insoluble protein-A in the form of formaldehyde fixated staphylococcus aureus (S. aureus) on the strain Cowan 1 was found to be useful as an anti-IgG reagent and has been used in a number of analytical techniques. Unspecific binding of the plasma proteins in such systems could be lowered by chemical immobilization of purified protein-A to beaded agarose (Sepharose) (Immunosorba®, Fresenius, Germany) or silica matrix (Prosorba®, Cypress Bioscience, USA). The production and purification of protein-A was facilitated as a methicillin resistant strain of S. aureus [9].

Protein-A binds all subclasses of human IgG, but its reactivity with subclass 3 is not total. The binding capacity of IgG 3, IgA, and IgM varies, therefore, in different individuals. Normally between 30 and 80 percent of the antibodies within these immunoglobulin classes react with protein-A [10]. In IA, the pathogens are bound specifically, generally no substitution fluids are needed and plasma can be conducted over the IA columns as often as needed to achieve any reduction

Table1: Therapeutic Apheresis (TA) immunologic diseases. (Category I: 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, Institutional Review Board (IRB) approval is desirable if TA is undertaken (15, 16).

	Apheresis Applications Committee of the ASFA (15, 16)		
	Category	**Recommen-dation grade**	**TA modality**
RPGN (ANCA associated) dialysis- dependence, - DAH	I I	1 C 1 C	TPE, IA-Protein-A, Peptid-Gam®, Tryptophan, Anti-human-Ig
Immune complex nephritis, dialysis dependence	III	2 B	
Anti-glomerular basement diseases (Goodpasture s.) dialysis-dependence - no DAH - DAH dialysis-dependence	III I I	2 B 1 C 1 B	
Focal segmental GN (FSGN) - primary - secondary - recurrent (in transplantated kidney)	 III III I	 1 B	
Renal transplantation - ABO compatible, ab mediated rejection, desensitization living donor - ABO incompatible, desensitization living donor humoral rejection, group A2/A2B into B decreased donor	I I I II IV	1 B 1 B 1 B 1 B 1 B	
Acute inflammatory demyelinating polyneuropathy (AIDP)	I	1 A	TPE, IA-Protein-A
Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)	I	1 B	
Multiple Sclerosis (MS) - acute MS - chronic MS	 II III	 1 B 2 B	
Pediatric autoimmune neuropsychiaric disorders associated with streptococcal infections (PANDAS), Sydenham´s chorea	I I	1 B 1 B	
Chronic focal encephalitis (CFE) (Rasmussen encephalitis)	III	2 C	
Acute disseminated encephalitis (ADEM)	II	2 C	TPE, IA-Protein-A
Lambert-Eaton myasthenic syndrome	II	2 C	
Miller-Fisher syndrome (MFS)	III	2 C	
Autoimmune hemolytic anemia - warm autoimmune hemolytic disease - cold agglutinin disease	 III II	 2 C 2 C	TPE; Exchange ECP, IA-Protein-A
Aplastic anemia - pure red cell aplasia (PRCA) - ABO incompatible HPC Tx	 III II - III	 1 B 1 B - 2 B	
Idiopathic thrombocytopenic purpura	III - IV	2 C	
Post transfusion purpura	III	2 C	
Coagulator factor inhibitors - alooantibody - autoantibody	 III – IV III	 2 B – 2 C 1 C – 2 C	
Systemic lupus erythematosus (severe), lupus nephritis	II IV	2 C 2 B	TPE, Tryptophan, IA-Protein-A, Dextran sulf., Peptid Gam®
Catastrophic antiphospholipid syndrome	III	2 C	
Rheumatoid arthritis	II	2 A	
Inflammatory eye disease	n.l.	n.l.	
Idiopathic dilated cardiomyopathy	II - III	1 B – 2 C	IA, TPE
Intraepidermal blistering pemphigus	III	2 B – 2 C	TPE, IA-Protein-A, ECP
Subepidermal blistering pemphigus	n.l.	n.l.	
Bullous pemphigoid	n.l.	n.l.	
D-penicillinamine induced pemphigus	n.l.	n.l.	
Progressive scleroderma	III	2 B – 2 C	
Pyoderma gangrenosum	n.l.	n.l.	

DAH: diffuse alveolar hemorrhage; HPC: hematopoietic progenitor cell; Tx: transplantation; n.l.: not listed; IA-Protein: immunoadsorption on protein-A (Immunosorba®, Prosorba®, Fresenius, Germany); Peptid-GAM® (globafin, Affina Immuntechnik, Germany); Tryptophan: immunoadsorption on tryptophan (Immunosorba, Asahi, Japan); Anti-human-Ig: Immunoadsorption on anti-human-immunoglobulin (Ig-Therasorb, PlasmaSelect, Germany); ECP: Extracorporeal Photopheresis; Peptid-GAM® (globafin, Affina Immuntechnik, Germany); Tryptophan: immunoadsorption on tryptophan (Immunosorba, Asahi, Japan); Dextran sulphate: chemical adsorption on dextran sulphate (Liposorber, Kaneka, Japan).

that one aims at, in some instances below the detection limit (e.g., HLA-antibodies in transplantation).

2. Anti-IgG immunoadsorption

Ig-Therasorb® immunoadsorption (Miltenyi Biotect, Germany) has been performed in a variety of clinical indications, especially in the treatment of autoimmune diseases. The system works on an antigen-antibody binding utility. The columns are reusable for the same patient for up to one year. After a primary separation of the blood into cells and plasma, the plasma of the patient is directed to one column where the selected components bind to the immobilized antibodies on the Sepharose. The mode of action of Ig-Therasorb is the specific binding of immunoglobulins and immune complexes by polyclonal antibodies. The matrix is Sepharose CL 4B coupled with specific antihuman-Ig sheep antibodies housed in a glass column.

3. Peptid-goat-antimouse (GAM®) adsorber

Peptides as ligands for immonadsorption exhibit several potential advantages over native proteins. Both newly developed adsorbers Coraffin® and Globaffin® are based on peptides covalently coupled to Sepharose CL-4B. The peptid-GAM® (Globaffin®, Affina, Germany) is the first synthetic adsorber. The adsorber contains synthetic peptid-goat-antimouse, which works like a minireceptor together with an epitop and binds all immunoglobulins independent from their antigen specify and thus, applicable in transplant recipients and several anti body mediated autoimmune diseases [11].

4. Immunoadsorption in idiopathic dilated cardiomyopathy (IDCM):

A variety of auto antibodies against different myocardial auto antigens have been identified in patients with IDCM. These include auto antibodies directed against the β1-adrenergic receptor, myosin, muscarinergic M2 receptor, Ca2+-ATPase, laminin. Cardiac auto antibodies have been shown to predispose patients to higher risk of arrhythmias and sudden cardiac death [12,13]. Therefore a special column, Coraffin® (Affina, Germany) was developed for the treatment of the IDCM. The special column contains a combination of synthetic peptides.

5. Different adsorbents

There are available immunoadsorption columns as adsorbents for the semi selective adsorption of anti-acetylcholine-receptor antibodies from blood or plasma. The adsorption material consists of a polyvinyl-alcohol gel, which contains covalently-bound tryptophan. There are also immune absorbers available for the semi selective treatment of systemic lupus erythematosus and multiple sclerosis. The adsorption material is polyvinyl-alcohol gel, which contains covalently bound phenylalanine [14]. Further possible indications are reported the anti-phospholipid antibody syndrome, rheumatoid arthritis, and bulbous pemphigus.

6. Immunologic diseases (Table 1)

Therapeutic apheresis was explored in the treatment of a variety of autoimmune syndromes. There are only a few prospective controlled trials available that are of adequate statistical power to allow definitive conclusions to be reached regarding the therapeutic value of TA. For those diseases for which the use of TA is discussed, the guidelines on the use of TA the Apheresis Applications Committee (AAC) of the American Society For Apheresis (ASFA) are cited [15,16].

Rapidly Progressive Glomerulonephritis (RPGN) is a diffuse glomerulonephritis that frequently begins acutely. RPGN is a histologic diagnosis including a number of etiologies such as Anti-Basement Membrane Antibody Glomerulonephritis (ABM-ab-GN), which is very rare, Antineutrophil Cytoplasma Antibodies (ANCA), and even IgA nephritis. Its histological characteristics are usually necrosis of the capillary walls and semi-lunar formation, and deposition of IgG and C3 along the glomerular basement membrane. Most cases

are simultaneously accompanied by acute kidney injury [5,17]. More than 90% of patients with RPGN due to Goodpasture/anti-GBM RPGN have anti-GBM antibodies in their circulation.

The incidence is 0.85 per 100 000/year. Importantly, when discussing RPGN, a number of entities are frequently included in case series and trials, thus confounding results [5]. Therapy consists of administration of high-dose corticosteroids (e.g., methylprednisolone) and cytotoxic immunosuppressive drugs (e.g., cyclophosphamide or azathioprine) [18]. Other drugs used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, and antibodies against T cells [5,17].

In anti-basement membrane antibody glomerulonephritis (Goodpasture Syndrome, ABM-ab-GN), antibodies appear that are directed against a peptide component of one of the two non-collagen parts of type IV collagen. However, type IV collagen is found not only in the kidney, but also in the vessels of other organs, such as the lung [5]. Only a small part of ANCA GN has anti-GBM ab, mostly it is thought to be an environmental or infectious exposure that triggers the onset of these diseases. ANCA GN responds to TPE even when the patient is on dialysis and anti-GBM GN does not.

Goodpasture syndrome is a rare autoimmune disease in which antibodies attack the basement membrane in the lungs and kidneys. The frequency of anti-GBM disease varies from 0.5 to 1 case per million populations [15] The formation of anti-basement membrane antibodies is frequently limited in duration. The auto antibodies cause severe disturbances in the permeability in the lung with significant deterioration in diffusion capacity and hemoptysis. The renal deposition of this autoantibody frequently leads to rapid deterioration in renal functioning, which expresses itself histological in a necrotizing glomerulonephritis in part [5].

The various forms of glomerulonephritis are treated with immunosuppression not only with corticoids, alkylating agents, and cyclosporine A, but also with combinations of almost all of these drugs [17]. The combination of corticoids, immunosuppressives, and TPE in varying combinations was the first step in improving the overall prognosis for RPGN. In subsequent years, RPGN has been treated with a combination of immunosuppressive drugs and IA with excellent results.

In immune complex nephritis of many types of glomerulonephritis are initiated by the deposition of immune complexes, which induce tissue injury via either engagement of Fc receptors on effector cells or via complement activation [19]. The generation of antibody and subsequent tissue deposition of ICs is thought to trigger the pathogenic consequences of systemic autoimmune disease. In view of the devastating pathophysiologic consequences of interaction between circulation immune complexes and the basement membrane, Pusey et al. recommended TPE for severe cases of immune complex nephritis [20].

Approximately 60% of patients with RPGN present with crescentic glomerulonephritis characterized by few or absent immune deposits, the so-called pauci-immune RPGN. Patients with this disease have either Wegner's granulomatosis, ANCA ab associated vasculitis, polyarthritis nodosa, or “renal-limited” pauci-immune GN. These diagnoses may represent a spectrum of manifestations of a single disease, because there is marked overlap of clinical and histopathological features, and several patients have ANCA in their blood, which are more common that anti-GBM. The concentrations of circulating ANCA correlate with the disease activity in some patients [5]. The prognosis of pauci-immune RPGN in general has been poor. Precise therapy therapeutic recommendations are difficult to obtain from the literature, because most series comprise patients with different types of RPGN. However, available data suggest that 80% of such patients progress to ESRD without therapy with high dose immunosuppression or cytotoxic drugs. Some trials have evaluated the efficacy of TA as an adjunct to conventional immunosuppressive in patients with pauci-immune RPGN [5,21,22].

The cause of Nephrotic Syndrome (NS) of various GN such as Focal Sclerosing Glomerulosclerosis (FSGN), membranoproliferative GN, mesangioproliferative GN etc. is most idiopathic [5]. There is evidence pointing to a

role of the immune system in pediatric minimal change glomerulonephritis. Finally, the induction of remissions by high doses of immunoglobulin G (IgG, 0.4 g/kg BW), corticosteroid, alkylating agents, or cyclosporine therapy provides indirect evidence for an immune etiology. None of these observations, however, provides direct evidence of immunologically mediated pathogenesis [3]. Other therapeutic measures for NS are anticoagulants, thrombocyte inhibitors, ACE inhibitors, immunosuppressive drugs, lipid reducers, rituximab, and diet [15]. In high-risk patients, pre-transplant TA appears to prevent or delay recurrence. TPE is started once recurrence is diagnosed. The number of treatments needed to control proteinuria, surrogate marker of FSGN, is quite variable and can reach dozens [19]. In the case of resistance to medication or severe progression of the disease, additional TA therapy should be considered, as a continuing treatment given once a week, or every 2 weeks, or once a month.

In chronic renal failure, kidney transplantation is the decisive alternative to permanent dialysis. Rejection of the transplanted kidney is a grave problem. Although various therapeutic interventions to delay or prevent rejection exist, steroids, immunoglobulins, immunosuppressives, cyclosporine A, OKT3, and other new developed immunosuppressive therapies are used. Infections and rejection reactions are the most frequent complications of modern transplantation [23]. Thus, acute kidney transplant rejection is considered to be an indication for TA [24]. TA is indicated in the management of rejection crisis due to preformed specific antibodies or a high degree of immunization [25].

Immunological problems like performed donor-specific antibodies or a high degree of immunization complicate the outcome of donor transplantation. Postoperatively the antibody-mediated rejection or drug-related side-effects of the medication can limit the therapeutic success of transplantation. Acute allograft rejection is one of the important complications after renal transplantation, and it is a deleterious factor for long-term graft survival. Rejection is a complex pathophysiologic process, which has been explained by transcriptome and proteome in RNA transcripts and proteins level, respectively [25].

Immunosuppression consists of tacrolimus, mycophenolate and steroids together with induction therapy with an IL-2-receptor blocking agent. The isoagglutinine antibodies against the donor can be eliminated. Firstly, the CD 19/20-positive pre-B cells with a single infusion of rituximab 4 weeks prior to transplantation and in a second step, the already existing antibodies are depleted by using TA such as TPE. Novel sensitization and production of antibodies is thereby efficiently prevented [26-28].

Therapeutic apheresis in transplantation as an important part of different therapy strategies like for therapy of several conditions such as Antibody-Mediated Rejection (AMR) or ABOi transplantation is accepted today. TA enables physicians to develop strategies to provide the best organ replacement to patients with high degrees of immunization or performed DSA, thereby expanding the use of living donation. The standard method has been TPE but it is increasingly being replaced by the more selective methods provided by DFPP or IA. TA is an important therapy for several kidney disorders [29].

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is an autoaggressive disorder that develops subsequent to infectious diseases and as a result of other noxae [3]. It is an acute polyradiculitis, which mostly affects the distal and proximal muscles of the extremities, as well as the trunk muscles and can progress with severe ascending paralysis, ending in respiratory paralysis [30]. Most patients with AIDP have inflammatory, predominantly demyelinating polyneuropathy [3]. This acute progressive disease, leading to rising paralysis, usually reaches its height within 1–2 weeks; 25% of all patients require artificial ventilation. AIDP occurs in one out of 50 000 persons each year in the industrial nations, regardless of gender or age.

The pathophysiologic mechanism has not been established completely, but in many cases, an antecedent infection by *Campylobacter jejuni* leads to the production of antibodies directed against certain

epitopes of the bacterium that also destroy the myelin sheath of the peripheral nerve. In recent years, researchers have applied a combination therapy of TPE or IA following by IgG (0.4 g/kg BW for 5 days [3].

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIPD) is an uncommon progressive or relapsing paralyzing disease caused by inflammation of the peripheral nerves [15]. Neurologic symptoms are decreased sensation, diminished or absent reflexes, elevated cerebrospinal fluid level, and evidence of demyelination [15]. The acquired disorder of the peripheral nervous system has probably an auto-immune pathogenesis. The nature of the responsible auto-antigens is unclear in most patients [31].

Recent clinical trials have confirmed the short term efficacy of IVIg, prednisone and TPE. Benefit following introduction of azathioprine, cyclophosphamide, cyclosporine, other immunosuppressive agents, and interferon-β and -α has been reported but randomized trials are needed to confirm these benefits [32]. If IVIg and corticosteroids are ineffective TA should be considered.

Multiple Sclerosis is a remitting chronic demyelinating disease of the CNS and is the most common cause of neurologic disability in young adults [33]. It has been estimated that some 120 000 to 140 000 patients are affected by MS in Germany. Worldwide, there are more than one million afflicted with the disease, and in the United States alone, there are more than 300 000 patients. MS is also diagnosed in children and adolescents. Estimates suggest that 8000–10 000 children (up to 18 years old) in the United States have MS, and another 10 000–15 000 have experienced at least one symptom suggestive of MS.

The definition of MS as an autoimmune disease is based on different characteristics [33]. The rationale for treating MS patients with TA derives from the presence of these circulating antimyelin antibodies, non-antibody demyelinating factors, aquaporin-4-specific serum auto antibodies, and neuroelectric blocking factors [16,33]. TPE removes antibodies and other humoral factors from the circulation safely and effectively. TPE has also been shown to increase the number and percentage of suppressor T cells and decrease the helper T cells in MS patients, thus effectively decreasing the ratio of elevated helper/inducer to suppressor/cytotoxic cell. Children should be treated with corticosteroids. If corticosteroids alone do not bring enough improvement, other treatments, including IVIg, interferon ß 1a, and TA, are available to treat to treat MS attacks.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Seydenham´s chorea (SC) are post-infectious neuropsychiatric disorders. Both are neuropsychiatric symptoms, which typically follow Group-A Beta-Hemolytic Streptococcus (GABHS) infection, and may have shared etiopathogenesis. Postulated pathogenesis suggests that streptococcal antigens induce antineural antibodies by an abnormal immune response [16]. GABHS infection has been associated with childhood-onset neuropsychiatric disorders, such as, obsessive compulsive disorder and tic disorders. The onset of PANDAS is acute and dramatic, presenting with emotional/mood lability, attention deficit, deterioration of handwriting, separation anxiety, tactile/sensory defensiveness, enuresis, cognitive deficits, and motor hyperactivity [15].

Sydenham's chorea is the main common acquired chorea of childhood. The major clinical manifestations are chorea, hypotonia, and emotional lability. The duration of SC is several months with a recurrence rate of about 20% [16]. The treatments for PANDAS include antibiotics and cognitive behavioral therapy. The severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol [15]. If these fail, corticosteroids may be tried. While children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis, the efficacy of penicillin prohylaxis in preventing symptom exacerbations in children with PANDAS remains doubtful. In severely symptomatic or refractory patients with PANDAS or SC, IVIg (1 g/kg per day for 2 days) or TPE has been shown to reduce symptom severity or shorten the course.

The chronic Focal Encephalitis (Rasmussen Encephalitis) is chronic encephalitis characterized by intractable focal seizures and slowly progressive neurological deterioration. Onset is typically in childhood with a mean age 6.8 ± 5.1 years but a similar syndrome has been described in adults, too. The etiology is unknown. Antecedent infection with Epstein–Barr virus, herpes simplex, enterovirus, or cytomegalovirus has been implicated. There is progressive loss of function in the affected cerebral hemisphere and cognitive decline [15]. Anticonvulsants are necessary but are not always effective in controlling the disease, nor do they stop its progression. Subtotal, functional complete hemispherectomy can markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia corticosteroids and IVIg given for up to 2 years in a tapering schedule to diminish epilepsia and other symptoms.

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine wether TPE is effective in postponing surgical therapy. An initial course of TPE may be followed by 2 days of IVIg 1 g/kg per day. Monthly IA of 1.5–2.0 TPV per treatment has been reported to be effective in one patient [16]. Confirmation of anti-GluR3 antibodies may support the use of TA in patients with Rasmussen's encephalitis.

Acute disseminated encephalomyopathy is an acute inflammatory monophasic demyelinating disease that affects the brain and spinal cord, which typically occurs after a febrile, viral prodrome or vaccination [15]. The pathogenesis is perhaps a disseminated multifocal inflammation and patchy demyelination associated with a transient autoimmune response against myelin or other autoantigenes. The typical symptom is that of multifocal neurological deficits such as ataxia, weakness, dysarthria, and dysphagia accompanied by change in mental status. Corticosteroids are the first-line therapy, which hasten recovery and result in clinical improvement in up to 60% of patients. IVIg is for patients who do not respond to corticosteroids [15]. TPE is used and has a clearly defined role. TPE removes presumed offending antibodies as well as through immunomodulation.

Lambert-Eaton myasthenic syndrome is a rare, but reasonably well-understood, antibody-mediated autoimmune disease that is caused by serum auto-antibodies and results in muscle weakness and autonomic dysfunction [16,34]. Like MG, Lambert-Eaton syndrome is based on a disorder of the transmission of neuromuscular excitation. In this case no acetylcholine is released.

Miller-Fisher Syndrome (MFS) is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. It is considered to be a variant form of Guillain–Barré Syndrome (GBS). Because MFS is classified as a variant form of GBS and has a close association with the presence of the anti-GQ1b antibody, one would expect the efficacy of treatment with TPE or IVIg to have been proved.

In the Stiff-Man syndrome, Brashear et al. found auto antibodies to GABAergic neurons that were removed by TPE and the patient improved [3].

Autoimmune Hemolytic Anemia (AIHA) is characterized by reduced erythrocyte in vivo survival time and by the presence of warm or cold agglutinizing antibodies against the autologous erythrocytes. Autoimmune hemolytic anemia is diagnosed by direct microscopic evaluation of the peripheral blood film, hyperbilirubinemia, reticulocytosis, positive direct antiglobulin test (direct Coomb's test), and elevated serum LDH [35]. Immune hemolytic anemia is a result of antibody fixation to a red cell antigen. This autoantibody triggers either intravascular red cell destruction mediated by the terminal lytic complement complex (C5b-C9) or extravacular destruction mediated by macrophage-phagocytic system [36].

Antibody removal by TPE is also effective here. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells [37]. TPE can remove effectively pathogenic immune complexes, activated complements, and auto antibodies [16]. The duration of the TPE treatment is until the hemolysis is controlled and the need for transfusions is limited.

Until now only some case reports of aplastic anemia, which have been treated with TPE, have been published. The pathogenesis of aplastic anemia is regarded as complex and mostly unclear. In some cases, hemopoietic and erythropoietic inhibitors have been found in serum, leading to it being considered an autoimmune disease [3]. In these patients it was possible to remove the circulating inhibitors by TPE. TPE is only indicated in the case of proven autoimmune pathogenesis. Successful therapy has also been conducted in recent years with cyclosporine A. Allogenic Hematopoietic Progenitor Cell (HPC) transplant is the treatment of choice for severe AA in newly diagnosed patients < 40 years old.

ABO Incompatible Hematopietic Progenitor Cell Transplantation: The presence of natural antibodies in the recipient against the donor's ABO blood group, which may cause hemolysis of red cells present in the transplanted product, is the requirement of the major incompatibility [15]. In peripheral hematopoietic progenitor cells that are collected by apheresis, there is a lower risk of hemolysis due to reduced red cell contamination (2–5%) as compared to HPCs derived from the bone marrow.

In minor incompatibility with passenger lymphocytes making antibodies 7–12 days after infusions, prophylactic red cell exchange with group O red cells can be performed to deplete recipient type red cells [15,16]. If unable to red cell deplete the HPC product, TPE should be performed before infusion of HPCs and the replacement fluid is a combination of albumin and plasma (50:50) compatible with both donor and recipient [15]. Before HPC transplantation, the goal should be to reduce the IgM or IgG antibody titers to ≤ 1:16 immediately. Generally, 2–4 TPEs are sufficient and if the antibody titer is high in the case of delayed red cell recovery or Pure Red Cell Aplasia (PRCA), TPE may be performed in the transplantation period.

Idiopathic Thrombocytopenic Purpura (ITP) is an inherited or acquired disease that results in a reduction of circulating thrombocytes. This condition may be asymptomatic or manifests itself in hemorrhagic diathesis with petechial bleeding. The immune thrombocytopenias are a heterogenous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies. ITP is caused by auto antibodies which, in severely progressing cases, are accompanied by hemorrhagic diathesis. ITP is the most common auto immune hematologic disorder. The etiology is still for the most part unknown. The spleen plays an important role, since it not only produces a large part of the antibodies directed against thrombocytes, but also breaks down the damaged thrombocytes. As the antibodies can pass through the placenta barrier, the fetus can also be affected [38]. In more than 60% of the patients, part or full remission can be reached with steroid therapy. Splenectomy and cytostatics are further therapeutic measures. In recent years, in addition to being treated with TPE [39], therapy-resistant, acute, and chronic cases have also been successfully treated with high doses of IVIg of 400 mg/kg BW/day. A further mechanism leading to platelet destruction in drug-induced immune thrombocytopenic purpura is the formation of antibodies against neoantigens expressed after adherence of the drug to the RBC membrane [40]. Alloimmunization is the cause of neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transplant purpura.

Acute abrupt onset ITP is seen in childhood, and often follows a viral illness or immunization. The majority of children require no treatment and in 80–85% of cases the disorder resolves within 6 months. Some 15–20% of children develop a chronic form of ITP, which, in some cases, resembles the more typical adult disease. Chronic ITP in childhood has an estimated incidence of 0.46 per 100 000 children per year and prevalence of 4.6 per 100 000 children at any one time [41,42]. This form of ITP affects mainly women of childhood age (female: male: 3:1). Childhood ITP has an incidence of between 4.0 and 5.3 per 100 000 [41].

The successful use of high doses of IgG and anti-D therapy has reduced TA to second-line or third-line treatment in these cases [42]. The second-line therapy is splenectomy and high dose corticosteroids, high dose

IVIg, intravenous anti-D, cyclosporine A and dapsone. Patients who failed the first- and second-line therapies must be treated with interferon-α (IFNα), rituximab, campath-1H, mycophenolate mofetil and TA [41]. TA can induce remissions in approximately 80% of patients with ITP. TA becomes a legitimate option for maintenance therapy in chronic ITP patients, if the application of IgG is not possible due to allergic reactions, Rh-negative status, or splenectomy.

The most important part of TA is to remove antiplatelet antibodies to prevent bleeding by keeping the platelet count above a critical level. The goal of therapy is to obtain sustained remission with a minimum platelet count of over 50 000 platelets/μL. The measurement of free antiplatelet auto antibodies is a useful test for determining whether TA is indicated and if so, to assess its efficacy. As some severely progressing cases of ITP do not respond to steroids and/or high doses of immunoglobulin, immunosuppressive drugs, TPE is indicated [41].

First-line therapies are oral corticosteroids, IVIg (1–2 mg of prednisone/kg per day, IVIg at 1 g/kg per day for 1–2 days), and IV anti-Rh (D) (50–75 μg/kg) [15,16]. If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is deferred to prevent overwhelming postsplenectomy infection or allow for spontaneous remission. Should no significant improvement be observed within one or two weeks (thrombocytes > 80 000/μL), then TA treatment should be commenced immediately. Treatment with two to four sessions of TPE per month can also have a positive effect in chronic cases. TPE is recommended prior to surgery in acute respectively chronic uncontrollable bleeding [3,36]. TPE and IA with Protein-A columns may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated [15].

Post-Transfusion Purpura (PTP) occurs when donor B lymphocytes and dendritic cells migrated as passenger cells to the recipient's system, where they undergo clonal expansion after “homing in” on, and producing alloantibodies to the incompatible HPA allele [43]. Post-transfusion purpura is a rare bleeding disorder caused by alloantibody specific to platelet antigens. The antibody against the human platelet alloantigen HPA-1a is responsible for most of the cases: The majority of affected patients are multiparous women who presumably have been previously sensitized during pregnancy [43]. Blood transfusions rarely have been implicated as the primary cause for alloimmunization in PTP. Thrombocytopenia is usually severe and resolves spontaneously within several weeks. The diagnosis is confirmed by demonstrating that the patient's serum contains antibodies to platelet-specific antigens. The treatment is high IVIg (0.4 g/kg BW/day for 2–5 days or 1 g/kg BW/day for 2 days) [3,43]. It possibly acts by Fc receptor blockade of reticuloendothelial system. The removal of HPA-1a alloantibodies by TPE results in a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIg therapy is not effective [3].

Hemophilia A is a defect of the endogenous coagulation system, either inherited or acquired. It includes diseases that result from reduction, lack, or malformation of the factors VIII, IX, XI, XII, or prekallikrein. Hemophilia A is the longest-known hemorrhagic diathesis. As a result of substitution therapy, 5–20% of hemophiliacs develop antibodies against factor VIII administered during the course of treatment. Factor VIII antibodies belong to the IgG immunoglobulin group [44]. Antibodies can, however, also occur spontaneously in older patients or after pregnancy. These are antibodies that are directed against the patient's own factor VIII and can lead to an acquired factor VIII deficiency. Hemophiliacs may become sensitized to concentrates of their deficient coagulation factors. This occurs in about 15% of hemophilic patients.

TA is indicated in severely bleeding patients classified as immunological high responders [45]. TA can be considered when plasma concentration of the inhibitors exceeds either 10 BM or 3 MiU. TA should be implemented prior to high-dose administration of human

VIII concentrates. The use of IA with anti-immunoglobulin columns may be safer and more effective. A further indication for TA is in cases where inhibitors occur after factor substitution to induce immune tolerance according to the Malmö or similar protocols. Serial TPE and simultaneous administration of factor VIII/IX concentrates, high-dose IgG (0.4 g/kg per day), and cyclophosphamide is recommended. Several types of IA methods have been used, although reports are mainly anecdotal, consisting of relatively small numbers of patients. But IA may be clinically effective and cost-effective and should be considered early in the treatment of patients [45].

Acquired Factor VIII (F VIII) Antibodies in Non-Hemophiliac Patients: Antibodies against factor VIII can occur in many diseases such as immunological diseases, after pregnancy, as a reaction to medication (e.g., phenylbutazone), skin complaints, tumours, and diabetes mellitus. In the case of most patients with acquired factor VIII antibodies, it is not possible to determine the cause. If the underlying disease is known and treated, a drop in antibody titer can be expected.

F VIII auto antibodies in non-hemophiliacs produce a condition sometimes called acquired hemophilia A. Acute bleeding complications are an indication not only for the application of highly dosed concentrated factor VIII, but also for the removal of circulating antibodies through TPE. Substitution with fresh frozen plasma also includes the administration of factor VIII. The advantage of TPE and IA is in its rapid removal of antibodies and absence of excessive antibody formation. A disadvantage is an increased risk of bleeding with TPE treatment, if anticoagulation becomes necessary. With IA a selective elimination of acquired factor VIII antibodies is available [46]. For coagulation factor inhibitors, the extracorporeal removal by IA is more effective than TPE [47].

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by hypergammaglobulinemia, the presence of various auto antibodies, and immunoregulatory alteration. Among the auto antibodies, anti-double-stranded (ds) DNA is highly specific for the disease and is thought to play an important role in its pathogenesis. Anti-ds DNA auto antibodies constitute a heterogeneous family with respect to avidity, cationic charge, immunoglobulin class, and complement-fixing ability [3].

SLE usually involves high-titer antinuclear antibodies of the IgG group. This antinuclear antibody group includes not only the anti-dsDNA antibodies but also auto antibodies against single-stranded DNA (ssDNA), histones (H1–H4), and non-histone proteins (e.g., Sm, nRNP, SS-A/Ro, SS-B/La) [3]. Thus, in addition to antinuclear antibodies, SLE patients possess, although less frequently, auto antibodies against cytoplasmic antigens (SS-A/Ro, SS-B/La, ribosomes, Golgi apparatus), phospholipids (e.g., cardiolipin), cytoskeletal proteins (e.g., cytokeratin, desmin, vimentin, neurofilaments), basement membrane, and various cell superior determinants of leukocytes, erythrocytes, and thrombocytes. The tissue damage is caused by deposition of circulating immune complexes in various organs. Primarily involved are the smaller and medium-sized arteries of the skin, joints, lungs, liver, brain, kidneys, glomeruli, peritubular renal capillaries, and epidermal basement membrane [48].

Systemic lupus erythematosus is a chronic inflammatory disorder. With its extremely variable range of symptoms, SLE can cause broadly varying clinical conditions, ranging from an acute attack with high temperature, anemia, leukopenia and thrombocytopenia, arthritis, exanthema, and polyserositis, to lasting isolated damage to the kidneys, bone marrow, and joints. The disease preferentially affects childbearing age females (ratio F:M 10:1) [3]. The course of SLE is often unpredictable, with many attacks and milder forms of SLE showing spontaneous remission. Renal involvement in SLE is associated with high mortality. TPE is particularly indicated in severe cases, such as: Rapid progression despite immunosuppressive therapy; renal involvement, e.g., proliferative glomerulonephritis and nephrotic syndrome; extremely acute generalized vasculitis; thrombocytopenia and leukopenia; pulmonary, cardiac, and cerebral involvement; pancreatitis [1,3].

Cyclosporin is a well known immunosuppressive drug that has been used successfully for many years to delay organ transplant rejection in particular. Cyclosporin A seems to be promising in the management of autoimmune diseases, and via a similar mechanism of immune suppression as observed in animal experiments and in vitro studies. Routine implementation of cyclosporine A in chronic SLE presents new therapeutic possibilities due to selective inhibition of T cell activity at a very early stage [49]. The prognosis for SLE with varying organ manifestations has been considerably improved in recent years due in part to very aggressive therapy schemes [3,50,51].

Antiphospholipid Syndrome (APS) is an autoimmune hypercoaguable state caused by antibodies against cell membrane phospholipids that provoke thrombosis in the arteries and veins. Antiphospholipid antibodies can be detected by measuring lupus anticoagulant and anticardiolipin antibodies [3]. Antiphospholipid antibodies are implicated in vascular thrombosis, thrombocytopenia, and recurrent fetal loss in patients with SLE. The etiology of thrombosis of the small and large vessels is not completely understood. Involvement of the kidneys in APS is possible. In addition to thrombosis of the great arteries and veins, microscopic thrombotic microangiopathy is typically observed on kidney histology. High levels of antiphospholipid antibodies in patients with SLE increase the risk of venous and arterial thrombosis, adverse cerebrovascular events, recurrent fetal loss, and other arterial thrombotic and embolic complications, such as superior mesenteric artery thrombosis and thrombocytopenia.

Catastrophic Antiphospholipid Syndrome (CAPS) is an acquired hypercoagulable state, an unusual variant of APS. CAPS is defined as the acute onset of multiple thrombosis in at least three organ systems over a period of days or weeks, in patients with serologic evidence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and/or anti-β2 glycoprotein I). The most commonly affected sites are small vessels of kidneys, lungs, brain, heart, and skin, although large vessel thrombosis can also be present [15].

The exact mechanism by which TPE exerts an effect in CAPS is not known, but removal of pathologic antiphospholipid antibodies, as well as cytokines, tumor necrosis factor-α (TNF-α), and complement, is thought to play an important role. In most reports in which the replacement fluid transfusion of natural anticoagulants such as protein C, protein S, and antithrombin is given, this may contribute to the overall benefit of this procedure. However, it has not been established if plasma transfusion alone would have similar benefits because this option has not been tested. The optimal treatment of CAPS is still debatable given that the condition is rare and there have been no relevant prospective studies. However, the therapeutic approach has to have three aims: to treat any precipitating factors, e.g., infection, organ necrosis; to prevent and to control ongoing thrombosis; to suppress excessive cytokine production [15].

TPE and IA are valuable treatment strategies in patients with refractory disease manifestations and in pregnancy. IA seems to have a favourable side-effect spectrum compared to TPE. There is a clear need to perform randomized controlled trial to evaluate efficacy, safety and tolerability of both treatment strategies in the treatment of SLE and CAPS [52-54].

Rheumatoid Arthritis (RA) is an autoimmune disease that affects approximately 1–3% of the population and results in considerable morbidity and debility [1]. A typical characteristic of RA is that the joints are affected, with accompanying extra-articular manifestations, such as vasculitis as well as spleen and lymph node involvement. Recent evidence supports a central role for activated T cells in its pathogenesis. In the inflamed joints of patients with RA, activated T lymphocytes accumulate as activated cells [55]. The etiology and pathogenesis of rheumatoid arthritis are still unclear for the most part. Most drugs have only limited efficacy.

In RA, which is a chronic multisystem autoimmune disease, the most characteristic feature is an inflammatory synovitis, it can be relapsing or persistent, usually involving peripheral joints in a symmetric distribution. In about 20% of the patients, there are extra-articular

features, too. The role of antibodies to cyclic citrullinated peptides in the pathogenesis and diagnosis has been increasing attention [15]. The goals of therapy for rheumatoid arthritis are: relief of pain; reduction of inflammation; protection of articular structures; maintenance of function; control of systemic involvement; healing of bone erosions. None of the current therapeutic interventions is curative, and all must be viewed as palliative, aimed primarily at relieving the signs and symptoms of the disease [15]. Medical management of RA can be divided conveniently into five groups of medications: Aspirin, other nonsteroidal anti-inflammatory drugs, and simple analgesics; low-dose oral glucocorticoids; disease-modifying antirheumatic drugs (e.g., methotrexate); cytokine-neutralizing agents (i.e., anti-TNF, anti-IL-1); immunosuppressive and cytotoxic drugs, and novel and effective biologic agents like rituximab [15, 55].

Because both cellular and humoral mechanisms are involved in the pathogenesis of rheumatoid arthritis, in recent years TPE, cryofiltration, lymphoplasmapheresis, and leukocytapheresis have been implemented in addition to immunosuppressive therapy in particularly severe cases [55,56]. The clinical results of cryofiltration, double filtration, IA, and leukocytapheresis are very encouraging; these methods could be a regular therapy for rheumatoid arthritis, particularly in those patients with poorly controlled disease on immune suppressive or anti-TNF therapy [56,57]. IgG antibodies and CICs can be selectively removed from the blood by perfusion of patient plasma through the columns of the IA. The removal or alteration of CICs by IA, could be immunomodulatory and potentially beneficial for patients with RA [58].

The current management and treatment of rheumatoid arthritis is first to use the above mentioned five groups of medications. A new class of drugs the biological agents can be used to target specific cells and cytokines. These drugs have been shown to reduce inflammation significantly and to retard the progression of joint damage in rheumatoid arthritis, thereby reducing symptoms and improving function [59]. Early clinical results of monotherapy using tocilizumab, anti-interleukin-6 receptor antibody, in rheumatoid arthritis were encouraging [58,60,61]. Therefore, TA is only indicated in severe cases of rheumatoid arthritis if all five groups of drugs have failed.

Inflammatory eye disease: when conventional therapy with cortisone or immunosuppressive drugs fails or is inadequate in the treatment of immune-mediated inflammatory eye disease with an auto immunologic pathogenesis, TA may be indicated and is increasingly being implemented with success.

Severe uveitis is potentially associated with visual impairment or blindness in young patients [62]. In posterior uveitis, progredient inflammatory processes can lead to morphologic changes in the chorioidea and retina, contributing to functional deterioration. In uveitis intermedia, inflammatory processes in the peripheral retina and in the area of the ciliary body require primary attention and aggressive treatment. In both cases, secondary destructive changes in the vessels can occur, causing reduced perfusion of the retina and chorioidea. Primary inflammatory vascular changes may lead to secondary morphologic chorioretinal changes, which may then further impair function. The inflammatory process and/or the reduced chorioretinal perfusion are important. Therefore, an anti-inflammatory/immuno-modulatory therapy, a hemorheologic therapy, or a combination of both treatments, should bring about improvement of the condition, insofar as no other specific therapy is indicated [3]. Detection of immune complexes or auto antibodies in uveitis is problematic. With improved microcirculation, the damaged tissue can recover. The immunomodulating mechanism of TA, which favours a prompter elimination of inflammation, increases ocular function, and reduces recurrence, has been clarified.

In recent years, the anti-TNF-α antibodies, infliximab and adalimumab, and others demonstrated significant efficacy in controlling uveitis associated with seronegative spondyloarthropathies and juvenile idiopathic arthritis [63]. The high cost and potential side-effects of the biologic agents have limited their current use to uveitis refractory to immunosuppression.

Idiopathic Dilated Cardiomyopathy (IDCM) is a severe, relatively common heart disease characterized by decreased myocardial contractility, dilation of the heart and progressive heart failure. The reported incidence is between 60 – 100 patients per million with a prevalence of 300 – 400 patients per million. To date, the etiology of IDCM is unknown and diagnosis is currently made by exclusion of known causes for secondary cardiomyopathy [12]. Dilated cardiomyopathy is the number one indication for heart transplantation. Therapy has been mainly symptomatically with ACE inhibitors, digitalis, diuretics, and more recently, beta blockers. Mechanical support or transplantation are treatment options at the end of the line and only suitable for selected patients with IDCM. Despite optimized drug therapy the prognosis for patients with IDCM remains poor. Fifty percent of the patients with IDCM die of sudden cardiac death due to arrythmias or thromboembolic events within two to three years of myocardial failure [12].

Dermatologic immune mediated diseases represent a heterogenous group of disorders associated with circulating auto antibodies against distinct adhesion molecules of the skin and/or mucosa. According to the level of split formation, the disorders can be divided in the intraepidermal blistering pemphigus, such as Pemphigus Vulgarise (PV), pemphigus foliates, and paraneoplastic pemphigus, and the subepidermal blistering pemphigoid diseases, such as Bullous Pemphigoid (BP), pemphigoid gestations, and dermatitis herpetiformis [64].

The incidences of autoimmune blistering skin diseases in Germany has doubled in the last 10 years, to about 25 new cases per million humans per year, because of improved diagnostic techniques as well as the aging of the population [64]. There are an estimated 2000 new cases of autoimmune blistering skin diseases per year. The incidence of pemphigus in Europe is one to two cases per million humans per year, and 80% have PV.

Pemphigus Vulgaris (PV) is a severe, chronic disease of the skin and mucous membranes with poor prognosis, dissecting, acantholytic blisters and erosion, characterized by the presence of antibodies against epidermal intercellular substance. PV is the classic example of autoantibody-induced immune dermatosis, which can be recurrent or relapsing. The specific IgG fraction of the pemphigus serum initiates acantholysis without complement. It is surmised that enzymatically induced destruction with plasminogen activator and pemphigus acantholysis factor occurs after binding of the pemphigus antibody to the surface of the epidermal cell [65].

Pemphigus vulgaris was associated with a high morbidity and mortality. Introduction of corticosteroids reduced the mortality rate from 70 to 100% to a mean of 30% [65]. However, long-term administration of high doses of corticosteroids can be associated with severe effects. Other therapeutic options include dapsone, gold, and systemic antibiotics. They are often used in combination with other immunosuppressant agents such as azathioprine, methotrexate, and cyclophosphamide. Recently newer therapeutic modalities such as TPE, Extracorporeal Photopheresis (ECP), mycophenolate mofetil, chlorambucil, dexamethasone-cyclophosphamide, IVIg therapy, and rituximab, anti-CD20 monoclonal antibody, have been investigated [15].

The rationale for introducing TPE in the treatment of PV is based on the presence of circulating pathogenic auto antibodies. TPE has been used in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease. TPE was used in patients in all age groups (13–80 years old). The duration of disease prior to using TPE ranged between 1 month and 25 years. The goal of TPE is to reduce the level of auto antibodies with subsequent improvement in clinical symptoms. The decline in autoantibody titers, anti-keratinocytes cell surface antibodies and anti-desmoglein 3, correlated with clinical response in many patients [65]. The antiepidermal antibodies, which usually belong to the IgG category, can be easily eliminated with TPE. The success rate of a combined therapy of immunosuppression with steroids and TPE is

then over 95% [3]. Standard therapy for PV is based on a combined administration of high-dosed glucocorticoids and immunosuppressive drugs. In patients with severe, life-threatening, or recalcitrant PV, stronger therapeutic options should be considered, such as "pulse-therapy" with discontinuous intravenous infusion of mega doses of immunosuppressive drugs over a short-time, TPE, and IA of pathogenic auto antibodies using the extracellular domain of the PV. IA has been successfully applied in patients with severe atopic dermatitis and high total serum IgE levels [66]. In recent years various immunoadsorption systems and immunosuppressive protocols have been used to reduce the circulating auto antibodies. With a single IA procedure, between 50 and 75% of the specific pemphigus anti-desmoglein IgG auto antibodies can be eliminated by different adsorbers [66].

In recent years Extracorporeal Photopheresis (ECP) has also been applied to patients with serious cases of pemphigus with considerable success [65]. The clinical response in patients who underwent ECP was observed after two to seven sessions (two daily procedures per cycle). The total number of cycles received varied from 2 to 48. The follow-up ranged between 4 and 48 months, and the disease was controlled in most patients [15]. TA protocols used in PV vary widely and have been usually based on the observed clinical response after each treatment.

The rare Bullous Pemphigoid (BP) is another form of subepidermal blistering pemphigus. 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 [64,65]. BP is a chronic dermatosis often associated with acute exacerbations, with formation of bullae blisters usually on inflamed skin, subepidermal blister formation, and antibodies against the epidermal basal membrane. The pathophysiology is regarded as being a consequence of the combined effect of antigen, antibody, complement, and inflammatory cells, whereby lyosomal enzymes actually destroy the basal membrane zone and induce subepidermal blistering [3]. It is still unclear whether bullous pemphigoid can be provoked by medication or ultraviolet light rays. It is also possible that destruction of the basal membrane zone with release of basal membrane antigens can cause a direct immunological response in predisposed people. Thus, BP can also occur in combination with other autoimmune disorders.

IA has been successfully applied in patients with severe BP and can be performed either with different single use or reusable adsorbers. The latter are much more effective than the former, enabling a 75% reduction of auto antibodies in a single IA and 95% reduction when IA is performed on three consecutive days [64,67]. Various protocols for the use of IA in BP have been tested in combination with immunosuppression [64,67]. In all studies, the introduction phase consisted of three or four IA treatments on consecutive days, usually with high-affinity adsorbers. All patients benefitted from the treatment. The main advantages of IA are its rapid clinical effect and effectively lower of the antibody levels and leads to rapid clinical responses in patients with immune bullous disorders [64,67]. Meanwhile, IA and rituximab have been established as further therapeutic options [66,67].

D-Penicillamine-induced Pemphigus, steroid-resistant pemphigus, should also be mentioned. This foliaceus-type disease with its high mortality rate, which can occur as a side-effect in long-term penicillamine therapy, is a particular indication for TPE [68]. The functioning mechanism by which this drug induces acantholysis of the epidermis has still not been clarified. It is generally believed that similar immunological processes are involved to those in pemphigus vulgaris. The final step in anti-Dsg induced acantholysis is the response of the keratinocytes to auto antibodies binding via downstream signaling events and eventual keratin filament retraction and apoptosis, as many signaling pathways have been implicated in anti-Dsg induced acantholysis [68].

Immunosuppressive therapy is directed at preventing or slowing the rebound of antibody and immune complex formation after TA so as to sustain the therapeutic effect, given that suppression of a rebound through renewed antibody synthesis is very important for the further

course of the disease. In recent years only case reports of D-penicillamine-induced pemphigus treated successfully with TA were reported. It is generally recommended to combine TA with immunosuppression. This time-consuming treatment has to be repeated in short time intervals. IA is the more specific therapeutic option, in which only the pathogenic IgG is depleted in the patient's plasma. IgG auto antibodies are adsorbed on anti-human IgG affinity agarose column. Resynthesis of IgG auto antibodies was inhibited by postapheresis IVIg, therefore the additional effect of IA is difficult to observe since IVIg has also an immunomodulatory potency [64]. A combination of IA and rituximab showed rapid and long-lasting response of concomitant immunosuppressive medication [69]. Rituximab 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, long-term hypogammaglobulinemia, and neutropenia with an overall mortality of 4 % [70].

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 [71]. 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 [72]. In over 40% of cases, this disease occurs together with ulcerative colitis. In the vessel walls of vasculitic lesions, granular IgG, C3, complement, and IgM deposits have been observed. PG is a noninfectious neutrophilic dermatosis that usually starts with sterile pustules, which rapidly progress to painful ulcers of variable depth and size with undermined violaceous borders. In 17 to 74% of cases, PG is associated with an underlying disease, most commonly inflammatory bowel disease, rheumatological or hematological disease or malignancy. Diagnosis of PG is based on a history of underlying disease, typical clinical presentation and histopathology, and exclusion of other diseases that would lead to a similar appearance. 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. Subcorneal pustular dermatosis is an uncommon relapsing symmetric pustular eruption that involves flexural and intertriginous areas; it can be idiopathic or associated with cancer, infections, medications, and systemic diseases [73,74].

Therapeutic efficacy of systemic treatment with corticosteroids and cyclosporine A is documented in the literature for disseminated as well as for localized disease and should be considered first-line therapy. In cases refractory to this treatment, alternative therapeutic procedures (e.g., systemic corticosteroids, and mycophenolate mofetil; mycophenolate mofetil and cyclosporine; tacrolimus; infliximab, or TPE) are recommended [75]. Despite recent advances in therapy, the prognosis of PG remains unpredictable.

Henoch-Schönlein Purpura (HSP) is a systemic vasculitis that affects vessels of a small caliber. 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 complexes activate the alternate complement pathway, resulting in inflammation and small vessel vasculitis [76].

Prospective randomized clinical studies proving treatment efficacy are still lacking. Spontaneous recovery even in patients with severe clinical and histologic presentation and of late evolution to chronic kidney disease in patients with mild initial symptoms renders it difficult for treatment protocols. Prospective international multicenter studies looking at determinants of clinical and histopathological evolution as well as possible circulating and urinary markers of progression are necessary [77,78].

Conclusion:

There are only a few prospective controlled trials

available to allow definitive conclusions. The prognosis of auto immune diseases with their varying organ manifestations has improved considerably in recent years due to very aggressive therapy schemes. These include TA in combination with immunosuppressive therapies and/ or biologic agents. Use of newer technologies, such as immunoadsorption, possibly in combination with recent biologics, might offer some new perspectives for extracorporeal treatment of systemic auto immune diseases.

But all mentioned therapeutic apheresis methods are still technically complicated and very expensive. A reduction in costs is a valid demand in view of the scarce resources available in the healthcare system. Commissions consisting of physicians, administration specialists and representatives of the health insurance funds and others nowadays decide at a "round table" who will be granted medical facilities and who will not; this is a clinical routine adopted only in Germany. Physicians are committed to helping all of the 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 represents a great demand 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 healthcare must intensify their cooperation in this respect.

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