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European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology

Alexander Enk[1], Eva Hadaschik[1], Rüdiger Eming[2], Gerhard Fierlbeck[3], Lars French[4], Giampiero Girolomoni[5], Michael Hertl[2], Stephen Jolles[6], Sarolta Karpati[7], Kerstin Steinbrink[8], Georg Stingl[9], Beatrix Volc-Platzer[9], Detlef Zillikens[10]

(1) Department of Dermatology, Ruprecht-Karls-University Heidelberg, Germany
(2) Department of Dermatology, Philipps-University Marburg, Germany
(3) Department of Dermatology, Eberhard-Karls-University Tübingen, Germany
(4) Department of Dermatology, University of Zurich, Switzerland
(5) Department of Dermatology, University of Verona, Italy
(6) Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK
(7) Department of Dermatology, Semmelweis University Budapest, Hungary
(8) Department of Dermatology, Johannes Gutenberg-University Mainz, Germany
(9) Department of Dermatology, Medical University of Vienna, Austria
(10) Department of Dermatology, University of Lübeck, Germany

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Summary

Background and objectives: Treatment of severe dermatological autoimmune diseases and toxic epidermal necrolysis (TEN) with high-dose intravenous immunoglobulin (IVIg) is a well-established procedure in dermatology. As treatment with IVIg is usually considered for rare clinical entities or severe cases, the use of immunoglobulin is not generally based on data from randomized controlled trials usually required for evidence-based medicine. Since the indications for the use of IVIg are rare, it is unlikely that such studies will be available in the foreseeable future. Because first-line use is limited by the high costs of IVIg, the first clinical guidelines on the use of IVIg in dermatological conditions were established in 2008 and renewed in 2011.

Methods: The European guidelines presented here were prepared by a panel of experts nominated by the EDF and EADV. The guidelines were developed to update the indications for treatment currently considered effective and to summarize the evidence for the use of IVIg in dermatological autoimmune diseases and TEN.

Results and conclusion: The current guidelines represent consensual expert opinions and definitions on the use of IVIg reflecting current published evidence and are intended to serve as a decision-making tool for the use of IVIg in dermatological diseases.

Introduction

Immunoglobulin preparations are obtained from the pooled plasma of between 3,000 and approximately 10,000 individual donors. Pooling is performed to provide a species repertoire representing all antibodies and also natural auto-antibodies.

Given the large number of donors the potential risk of transmission of infectious agents such as viruses must be borne in mind. In order to ensure a high level of quality and maximum safety, all manufacturers of preparations derived from human plasma must adhere to European guidelines when obtaining and processing plasma. The Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency (EMA) and the Monograph in the European Pharmacopoeia govern writing and regular updating of these guidelines.

The following issues are regulated: how plasma is obtained, the screening of donated plasma, viral safety issues, methods of biological and pharmacological characterization and the testing of end products for clinical efficacy. The national authorities are responsible for authorizing the preparations, in that they carry out testing and define from which countries blood and plasma may be obtained. The national authorities are also responsible for the regular inspection of the manufacturing process and for virological testing, as well as for the approval of any changes to the manufacturing process.

The manufacturing pathway for immunoglobulin preparations starts with the identification of suitable donors. These donors must be healthy and must not have any signs of infections or chronic diseases. All plasma donations must be free of HBs antigen and anti-HCV antibodies as well as negative for HIV-1 and HIV-2 antibodies. All plasma donations are also subject to a "lookback" procedure with a holding period of at least 60 days. Any seroconversion of a donor occurring during this time can thus be detected and all stored plasma from the donor quarantined will be destroyed. Nucleic acid amplification technology (polymerase chain reaction; PCR) is used to screen the plasma from individual donors as well as the resulting plasma pool for the presence of HCV RNA, HBV DNA, HIV RNA, HAV RNA and Parvovirus B19 DNA. In the event of a reactive finding, the relevant plasma donations will be rejected/the plasma pool destroyed. Besides immunoglobulin concentration steps, plasma processing includes several independent process steps for virus inactivation/removal. A range of both enveloped and non-enveloped model viruses are used to spike the test preparations in order to quantify and validate the log reduction in virus of each individual step in the process. In addition to the antiviral properties of the manufacturing processes there are a number of dedicated steps for virus inactivation/removal which vary between manufacturers. For each batch of immunoglobulin manufactured, a certificate is produced which provides information on the main biological and pharmacological properties, the degree of purity and the antibody spectrum.

Besides viral safety, the clinical efficacy of the immunoglobulin preparations is also tested during this manufacturing process. Testing of functional integrity, determination of neutralizing antibodies and monitoring of immunomodulatory inflammatory properties is carried out on the basis of established test methods. Studies are also required in patients with primary antibody deficiencies. The successful treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP) is considered as evidence of the immunomodulatory activity of a preparation.

All the IVIg preparations which are commercially available at the present time consist of intact IgG molecules with an IgG subclass distribution which corresponds to the normal range. The half-life of IVIg in normal individuals is approximately three weeks. The F_C region of the IgG permits interaction and signal transduction by F_C gamma receptors on a range of immune cells. The mechanism(s) of action of immunoglobulins is complex and has not been elucidated completely in vivo. There has been significant progress in understanding the multiple potential mechanisms of action of immunoglobulin and it is likely that in any particular condition more than one mechanism may be operative. The roles played by F_C receptors such as the inhibitory receptor Fc RIIB, the effects of Fc sialylation, as well as changes in regulatory T cells (Tregs) and the TH17 pathway have received recent attention [1–4]. Immunoglobulins have been used for more than 50 years in the treatment of diseases associated with primary and secondary immune deficiency. Side effects of the current generation of products are generally considered to be minimal, however when using high dose therapy physicians should be aware of uncommon serious adverse events such as thromboembolic complications. In dermatology, IVIg is used mainly in the treatment of autoimmune diseases and toxic epidermal necrolysis [5] (Table 1). Although the list of diseases treated is long, it is generally based on small series or isolated case reports in uncontrolled studies. This is partly because the number of patients with these rare conditions is too small for large studies and it is usually difficult to compare the patients because of the very heterogeneous clinical courses and because of the concomitant medication used. As a result of the high costs of treatment, use of the preparations has to be highly selective, which makes it even more difficult to find large case series.

The aim of the current guidelines was to answer the following questions for each clinical condition:

1. Diseases for which IVIg is indicated?
2. Use of IVIg as first- or second-line treatment?
3. Initial duration of treatment?

Table 1 Indications for the use of IVIg.

Indications for the use of IVIg
severe forms of dermatomyositis, inclusion body myositis, polymyositis
toxic epidermal necrolysis
severe forms of autoimmune blistering diseases
severe systemic vasculitic syndromes
severe forms of lupus erythematodes
scleromyxedema
Less obvious indications
atopic dermatitis
autoimmune urticaria
severe forms of collagen vascular diseases
livedoid vasculopathy

4. Interval between IVIg infusion cycles?
5. Dosing of immunoglobulin therapy?
6. Duration of treatment per IVIg cycle?
7. Methods available for assessing therapeutic efficacy?
8. Long-term treatment advisable?

Dermatomyositis

Dermatomyositis is the condition in which the highest level of evidence exists for treatment with IVIg besides pemphigus vulgaris [6]. There are numerous individual case reports and small case series [7] as well as a double-blind, placebo-controlled crossover study, which demonstrate the efficacy of IVIg [8]. The following criteria were drawn up by the European Guidelines working group:

1. ***Indications:*** All severe forms of dermatomyositis, inclusion body myositis and polymyositis represent indications for the use of IVIg [9]. This applies also to what is referred to as idiopathic, paraneoplastic or juvenile forms [10], respectively.
2. ***Timing of treatment:*** The data available for these diseases justifies the early use of IVIg in dermatomyositis. In patients with a fulminant course, severe myolysis or paralysis, first-line treatment with immunoglobulins may be justified. As a general rule, IVIg should be used as a second-line treatment if steroid monotherapy has failed to produce an improvement after one month, or if reducing the steroid dose below an acceptable level results in a flare-up of the disease, or if side-effects prevent further steroid medication.The use of IVIg therapy is considered to be an adjuvant treatment with continuation of immunosuppressive therapy with corticosteroids and possibly also other immunosuppressive agents [11]. IVIg monotherapy has generally been less effective. From the immunological perspective, sufficient bone marrow function needs to be available given the concomitant immunosuppressive therapy. Therefore, treatment onset should not be delayed for too long.
3. ***Initial duration of treatment:*** Initial treatment should be carried out over a period of six months in order to determine the efficacy of treatment with IVIg. If therapeutic efficacy has not been achieved after six treatment cycles, the IVIg treatment should be discontinued. After 18 treatment cycles, a washout period should be attempted. It is possible to increase the interval between infusions to a maximum of six weeks beforehand (Figure 1). In the event of recurrences, treatment can be resumed at any time. This recommendation needs to be adapted to the course of disease for each individual patient (some patients need longer treatment).
4. ***Interval between infusions:*** Initially, adjuvant IVIg therapy should be administered every four weeks. If a good clinical response is achieved, the interval can be increased gradually to a maximum of six weeks. Longer intervals between infusions are not recommended because of the half-life of IVIg (approximately 3 weeks).
5. ***IVIg dosing:*** The bulk of evidence with respect to the use of IVIg in dermatological autoimmune diseases has been obtained with a dose of 2 g per kg body weight per treatment cycle. Because there is no clear evidence of efficacy with lower doses, adherence to the aforementioned dose recommendations is advised in these serious diseases (Table 2). Although there has been one report on the successful use of subcutaneously applied Ig in polymyositis and dermatomyositis in seven patients, this study awaits confirmation in larger patient cohorts [12]. Therefore s.c. Ig cannot generally be recommended in dermatomyositis.
6. ***Period of IVIg administration:*** Administration of the immunoglobulin should be spread over 2–5 consecutive days. Tolerability is generally better with greater dose

Table 2 Recommended dosage regimens.

Recommended dosage regimens	
Dosage	Total 2 g/kg body weight*, applied over a period of 2–5 days
Treatment interval	Initially every four weeks/after six months gradually increase to 6-week intervals**
Long-term therapy	In individual cases

*3 g/kg body weight in toxic epidermal necrolysis.
**Only 1 cycle in Kawasaki´s disease and toxic epidermal necrolysis.

fractionation. In patients with cardiac or renal impairment, immunoglobulin preparations should be administered over a longer period of time. If the treatment is well tolerated at the beginning, it can generally also be carried out on an outpatient basis.

7. ***Evaluation of therapeutic efficacy:*** The clinical picture is the most important parameter for evaluating the efficacy of treatment in dermatomyositis, with evaluation of muscle strength playing the most important role. Autoantibody titers, on the other hand, do not reflect the response to treatment. In general, creatine kinase and muscle aldolase levels also return rapidly to normal under immunosuppressive therapy. This prohibits their use as indicators of efficacy. MRI or ultrasonography of the proximal muscle groups is important for the initial diagnosis as is specific muscle biopsy, but are unsuitable for close monitoring. The criteria for evaluating the clinical response is therefore normalization of muscle strength with gradual tapering of the steroid dose, fading of erythema and gradual resolution of other parameters such as Gottron's papules while on IVIg therapy. It is our experience that a response can be detected from the second treatment cycle on, mainly by the patient (especially on the basis of the improvement in muscle strength) but also by the treating physician. Nevertheless, tapering the concomitant medication too rapidly should be avoided. Between three and four treatment cycles are often required before a significant improvement in symptoms is seen and in severely affected patients, extension of treatment intervals needs to be done with care.
8. ***Long-term IVIg therapy:*** In rare cases, long-term therapy may be necessary in patients with severe dermatomyositis and a prolonged course, although therapy-cessation periods should be attempted to allow the effects of the IVIg therapy on the course of the disease to be assessed.

Autoimmune blistering diseases

The autoimmune blistering diseases are autoantibody-mediated disorders, the autoantigens of which are largely known and have been molecularly characterized. Autoimmune blistering diseases are generally treated by dermatologists only and are therefore of great importance for our speciality. The following recommendations were drawn up for the use of IVIg in these diseases:

1. ***Indication:*** All severe forms of autoimmune blistering diseases, which are refractory to therapy or relapsing after therapy [13] represent an indication for the use of IVIg. In fact, a randomized controlled trial [14] as well as an extensive literature review [15] have confirmed these evidence levels. The experiences are particularly good in pemphigus vulgaris, pemphigus foliaceus, mucous membrane pemphigoid [16] and epidermolysis bullosa acquisita. However, the use of IVIg may also be indicated in severe forms of bullous pemphigoid, linear IgA disease, IgA pemphigus or paraneoplastic pemphigus.
2. ***Timing of treatment:*** On the basis of the scientific evidence available, the use of IVIg cannot be recommended as a first-line treatment. However, contraindications to standard immunosuppressive therapy (e. g., aseptic bone necrosis, poorly controlled diabetes or advanced osteoporosis and cataracts) may justify the use of IVIg as a first-line treatment in isolated cases. Consequently, immunoglobulins should primarily be used as a second-line treatment following sufficient combination therapy with steroids (e. g. prednisolone 1–2 mg per kg body weight per day) and another immunosuppressive agent, e. g. azathioprine or mycophenolate mofetil [17, 18]. Here again, IVIg is an adjuvant therapy, which must be administered while continuing the conventional immunosuppressive therapy. IVIg may also be considered in patients treated with rituximab in whom sufficient disease control was not attained. This also means that immunoglobulin use should not be delayed for too long because adjuvant treatment is useful only with concomitant immunosuppressive therapy and this requires adequate bone marrow function. Monotherapy with immunoglobulin is generally not recommended.
3. ***Initial duration of treatment:*** Treatment should be administered initially for a period of between 3–6 months in order to assess the efficacy of the IVIg in each individual case. Some patients do not show a definitive sustained response until they have undergone up to six cycles of treatment. If a therapeutic response cannot be documented after six cycles of therapy IVIg treatment should be discontinued (Figure 1). This recommendation needs to be adapted to the course of disease for each individual patient (some patients may need longer treatment).
4. ***Interval between infusions:*** Adjuvant therapy with IVIg should be administered every four weeks initially. If the clinical response is good, the interval between infusions can be increased gradually to a maximum of six weeks. Longer intervals are not recommended because of the half-life of IVIg.
5. ***Dosing:*** As already mentioned above, most studies have used a total dose of 2 g per kg body weight by intravenous infusion. Because only insufficient data are available at present for higher or lower doses, this dosage should be considered as the standard recommendation at present (Table 2).
6. ***Period of treatment:*** As already mentioned above, treatment should be administered over a period of 2–5 days, with fractionated administration of the IVIg therapy contributing to better tolerability.

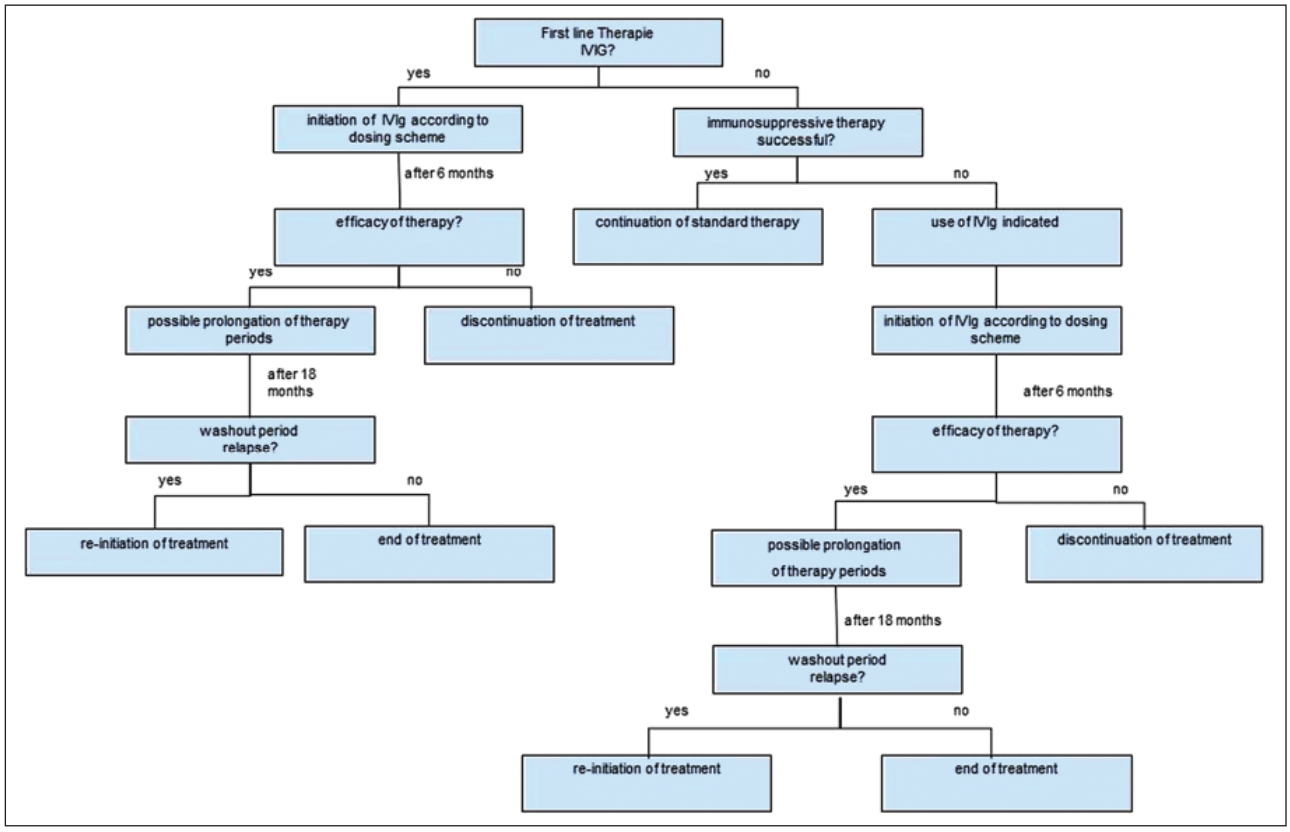

Figure 1 Decision Tree for the use of IVIg for treatment of severe autoimmune diseases in dermatology.

7. ***Evaluation of treatment efficacy:*** Both clinical and serological parameters are used for evaluating the efficacy of treatment in most blistering autoimmune diseases. The criteria for evaluating the clinical picture are therefore cessation of blistering and healing of existing lesions under adjuvant IVIg therapy. At the same time, a moderate reduction in concomitant immunosuppressive treatment should be possible without recurrence. Serological parameters such as IgG autoantibody titers measured by ELISA or indirect immunofluorescence microscopy may provide an additional parameter to evaluate the therapeutic efficacy of IVIg.
8. ***Long-term therapy:*** Long-term therapy with IVIg is recommended only in rare cases especially when mucous membranes are severely affected. An exception to this are patients in whom disease recurrence occurs after withdrawal of IVIg therapy and no other treatment options exist and if this is the case combination therapy with rituximab may be considered. Regular washout periods should be attempted.

Vasculitic syndromes

Vasculitic syndromes are systemic inflammatory conditions which affect the blood vessels of one or more organ system. A distinction is made between primary and secondary systemic vasculitic syndromes. Because the skin is often involved as an indicator organ and the conditions often prove highly refractory to treatment, immunoglobulin is often considered as a therapeutic alternative. The following recommendations can be made on the basis of our current state of knowledge:

1. ***Indication:*** Kawasaki's disease is the only disease in this category for which IVIg is first line treatment. In all other cases, primary treatment generally consists of high-dose corticosteroids together with additional immunosuppressive agents such as cyclophosphamide or others. The use of these aggressive immunosuppressive regimens is often associated with severe side effects, and recurrences occur on withdrawal or dose reduction. In patients who do not respond to standard therapy or those with a particularly fulminant progressive disease, IVIg therapy may be considered as an early treatment option. All forms of severe vasculitis [19] can represent potential indications for IVIg [20]. Particularly positive results have been achieved in primary vasculitis, e. g. chronic polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, IgA-associated vasculitis, Churg-Strauss disease [21], microscopic polyangiitis, and in

secondary autoimmune vasculitis. Good results have also been achieved in patients with anti-phospholipid antibody syndrome [22].

2. ***Timing of treatment:*** IVIg is only approved for Kawasaki´s syndrome as a first-line treatment. As already mentioned above, treatment in all other indications is considered as adjuvant therapy only after failure of immunosuppressive therapy or in the presence of contraindications. The early use of IVIg may, however, prevent massive tissue destruction and thus reduce the extent of damage in conditions such as hemorrhagic necrotizing vasculitis of the skin or in Wegener's granulomatosis.
3. ***Initial duration of treatment:*** As with the aforementioned indications, a treatment period of 3–6 months is useful initially in order to obtain a clear idea of the response to treatment (Figure 1).
4. ***Interval between infusions:*** As described above, treatment should be administered at 4-week intervals initially. If the clinical response is good, the intervals between infusions can be extended gradually to a maximum of six weeks. A clear benefit of longer treatment intervals has not been documented.
5. ***Dosing:*** The recommended dose for the treatment of Kawasaki syndrome in children is again 1.6–2 g per kg body weight per treatment cycle (as bolus infusion or divided into single infusions given over 2–5 days 2) in addition to the recommended administration of acetylsalicylic acid with an initial dose of 50 mg/kg body weight per day. On the basis of this, all case series of patients with systemic vasculitic syndromes have so far been treated with a total dose of 2 g per kg body weight (Table 2).
6. ***Duration of treatment:*** Treatment should be administered over a period of 2–5 days, with a longer duration of treatment being associated with fewer side effects. In the case of systemic vasculitis with renal involvement in particular, the infusion rate should be reduced or possibly a reduced dose should be used (e. g., a total of 1 g per kg body weight).
7. ***Evaluation of treatment efficacy:*** The clinical response should be the main criterion used for evaluating therapeutic efficacy. Because organ involvement is rather heterogeneous, only general recommendations can be expressed here. The pattern of CRP and organ-specific laboratory tests, can be used as indicators of response. As an example, in Wegener's granulomatosis, the c-ANCA titre and level of the proteinase 3 (PR3) ELISA can be used as additional indicators.
8. ***Long-term therapy:*** Long-term therapy with IVIg is recommended only in exceptional cases.

Lupus erythematosus and other collagen vascular diseases

Almost all autoimmune connective tissue diseases have already been treated experimentally with IVIg in small series. The best data exist for systemic lupus erythematosus. The following recommendations are proposed:

1. ***Indication:*** All severe cases of lupus erythematosus can represent an indication for attempted treatment with IVIg if no other treatment options are available. Its use in systemic lupus erythematosus, especially in lupus nephritis [23], is considered effective. Less clear are the data in patients with scleroderma, in which no clear recommendation can be expressed [24]. Care should be taken in the setting of connective tissue disease as the infusion of IVIg in patients with high titre rheumatoid factor (RF) has been associated with renal damage.
2. ***Timing of treatment:*** The use of IVIg is generally not a first-line treatment option. Previous combination treatment with steroids and another immunosuppressive associated with a poor response or severe complications is considered an indication for the use of IVIg. Again, however, the use of IVIg should not be delayed for too long in conditions such as lupus nephritis to avoid tissue damage. Here too, treatment should be given in combination with adequate immunosuppressive therapy.
3. ***Initial duration of treatment:*** As with the aforementioned conditions, application of IVIg is initially recommended over a period of six months. If there has been no response to treatment after this time, treatment should be discontinued.
4. ***Interval between infusions:*** The initial interval between infusions should again be four weeks. The interval between the individual bolus infusions can then be increased gradually to six weeks. Any additional increase in the interval is not useful because of the half-life of immunoglobulin.
5. ***Dosing:*** Again, the only experience available in the conditions listed above is with the standard dose of 2 g per kg body weight. This should be adopted as the standard recommendation (Table 2).
6. ***Treatment period:*** Treatment should be administered over a period of 2–5 days. In the case of severe organ involvement such as kidney or heart involvement in particular, the treatment period should be increased to five days.
7. ***Evaluation of treatment efficacy:*** The focus is again on the clinical evaluation of treatment efficacy. Because this is a very heterogeneous group of diseases, it is only possible to express the general recommendation that improvement in primary organ involvement (e. g. protein

excretion in the urine) should be used as an indicator of response. In isolated cases, the pattern of disease-specific autoantibodies such as double-strand DNA antibodies can be used as an indicator of response in systemic lupus erythematosus.

8. ***Long-term therapy:*** Long-term therapy can be recommended only in exceptional cases.

Scleromyxedema

Scleromyxedema is a severe multi-organ condition characterized by fibroblast proliferation and mucin deposition in skin and internal organs associated with monoclonal gammopathy in the majority of cases. Thickening and fibrosis of skin often cause a debilitating situation and internal organ involvement can put the patient's life at risk [25, 26]. Scleromyxedema is refractory to most classical immunosuppressive therapies, but responds quickly to treatment with IVIg as documented in many case reports and in small case series [27, 28]. The body of evidence on efficient therapy of scleromyxedema with IVIg has substantially grown since the first report of efficacy in 2000 [26, 29] leading to the addition of this disease to the current guidelines. The following recommendations are proposed:

1. ***Indication:*** All severe cases of scleromyxedema represent an indication for a treatment attempt with IVIg as treatment with other immunosuppressive agents is often not effective. Its use in scleromyxedema is considered effective [26, 30, 31].
2. ***Timing of treatment:*** IVIg should be considered treatment of choice in refractory cases of scleromyxedema with either fast deterioration of skin symptoms, the dermato-neuro syndrome or life-threatening involvement of internal organs. In milder cases, initial treatment with immunosuppressive regimens should be undertaken. Failure to respond to such treatment or contraindications to such treatments justify initiation of treatment with IVIg. In scleromyxedema no additional treatments are needed besides IVIg.
3. ***Initial duration of treatment:*** As with the other conditions, the use of IVIg is initially recommended over a period of six months. If there has been no response to treatment after this time, treatment should be discontinued.
4. ***Interval between infusions:*** The initial interval between infusions should be four weeks. The interval between the individual bolus infusions can then be increased gradually to six weeks. Any additional increase in the interval is not useful because of the half-life of immunoglobulin.
5. ***Dosing:*** Most experience in scleromyxedema exists with the standard dose of 2 g per kg body weight. This should be adopted as the standard recommendation (Table 2).
6. ***Treatment period:*** Treatment should be administered over a period of 2–5 days. In the case of severe organ involvement such as kidney or heart involvement in particular, the treatment period should be increased to five days.
7. ***Evaluation of treatment efficacy:*** The focus lies on the clinical evaluation of treatment efficacy. As skin involvement is present in nearly all cases and responds very well to treatment with IVIg, it should be used as an indicator of response. In isolated cases, clinical response to CNS or internal organ involvement can be used as additional indicator of response in scleromyxedema.
8. ***Long-term therapy:*** It has been documented in several cases that after discontinuation of IVIg there are relapses [26, 32]. If a relapse is severe and life-threatening, long-term therapy can be recommended in exceptional cases.

Toxic epidermal necrolysis

Toxic epidermal necrolysis represents a life-threatening side effect of drugs [33]. The condition is associated with Fas (CD95) and granulysin-mediated apoptosis, as well as annexin A1-mediated necroptosis of epidermal keratinocytes [34]. Therefore it is assumed that antibodies interfering with these apoptotic pathways (and contained in IVIg preparations) might be beneficial in this disease [35]. Because of its life-threatening and fulminant progressive course with detachment of large areas of the epidermis in severe cases, these patients are at acute risk of infection and must receive intensive care. The condition is nevertheless lethal in up to 40 % of cases. The following recommendations have been drawn up for the use of IVIg:

1. ***Indication:*** In certain studies the early administration of high doses of IVIg in toxic epidermal necrolysis was suggested to be potentially life-saving. A systematic review and meta-analysis of observational controlled studies published before 31 July 2011 indicated that high-dose IVIg (≥ 2 g/kg) was associated with significantly lower mortality than low-dose IVIg (< 2 g/kg, $p = 0.022$) [36]. The pooled odds ratio for mortality in patients treated with IVIg (all doses confounded) versus supportive care was however not significantly reduced at 0.63 ($p = 0.27$). A subsequent meta-analysis of 13 published studies between 1996–2011 in which severity of disease had been determined with SCORTEN, revealed again a non-significant reduction in standardized mortality rate of 0.322 ($p = 0.155$) in patients treated with IVIg (all doses confounded), but a strong and significant inverse correlation between IVIg dosage and standardized mortality rate ($p = 0.009$), showing that IVIg at dosages of ≥ 2 g/kg significantly decreased mortality compared to that expected in patients with SJS or TEN [37]. Although the mechanism of action remains

unclear, the early administration of high-dose immunoglobulin may be considered in confirmed cases of toxic epidermal necrolysis in the absence of an alternative evidence-based therapeutic alternative given that the potential benefits of high-dose IVIg outweigh the risks of the of the medication and the diseases natural course.

2. ***Timing of treatment:*** Unlike in the aforementioned conditions, IVIg should be administered as soon as possible after confirmation of the diagnosis. IVIg treatment can then be administered as monotherapy in addition to supportive measures including intensive care. The concomitant administration of corticosteroids or immunosuppressive agents is controversial.
3. ***Initial duration of treatment:*** Only one cycle of treatment is usually required in this condition, administered over a period of 3–5 days.
4. ***Dosing:*** The dose recommendation in toxic epidermal necrolysis differs from that in autoimmune diseases. A total dose of at least 3 g per kg body weight is generally recommended (Table 2). Fractionated administration (over 3–5 days) is required, particularly in the case of risk factors including renal impairment, pre-existing cardiovascular disease and diabetes in these patients.
5. ***Evaluation of treatment efficacy:*** The cessation of ongoing epidermal detachment and the onset of re-epithelialization are good clinical parameters for evaluating treatment efficacy, but survival remains the most valid clinical outcome measure. The contribution of IVIg to the healing process is difficult to assess.
6. ***Long-term therapy:*** Not applicable.

Other possible treatment indications

IVIg has been described as an effective treatment method in numerous clinical conditions in dermatology (Table 1). Some of the more frequent entities will be mentioned here, although a conclusive assessment is not possible at present.

Atopic dermatitis

According to the literature available and isolated case reports, the use of IVIg should definitely be considered in the most severe forms of atopic eczema. According to reports in the literature, healing can in some cases be significantly accelerated in cases which are refractory to conventional treatment [38, 39].

Autoimmune urticaria

The use of immunoglobulin can also be considered as a last resort in severe cases of autoimmunologically mediated urticaria. Only single case reports and smaller case series are available at present in this indication, and these describe the successful use of immunoglobulin at the aforementioned standard dose [39]. A conclusive assessment of these reports is not possible at the present time and newer therapies including anti-IgE monoclonal antibodies may play a greater role in therapy-resistant urticaria in the future.

Pyoderma gangrenosum

The use of IVIg can be considered as an option in severe refractory cases of pyoderma gangrenosum. As only small case series are available at present time, no general consensus statement is possible at present time.

Livedoid vasculopathy

Numerous case studies have reported on the successful use of IVIg in therapy-resistant livedoid vasculopathy [40, 41]. Although no general recommendation can be given at this point, the amount of evidence for a positive effect of IVIg is increasing, justifying their use in desperate cases.

Summary

The treatment recommendations presented for the use of IVIg in dermatology highlight the importance of IVIg therapy in numerous defined dermatological autoimmune diseases and in toxic epidermal necrolysis. The value of IVIg therapy in diseases which are otherwise refractory to treatment is undisputed. Clear treatment recommendations can therefore be given for the diseases described above. Because the exact mechanisms of action of IVIg in vivo are still unclear in these conditions, further efforts should be made to launch randomized controlled trials despite the rarity of some of the disorders described. The current guideline recommendations are intended to create a basis for future randomized controlled trials. The implementation of this EU guideline in general practice means that the use of IVIg in dermatology will be optimized throughout Europe.

Methodology/Additional information

The European Guidelines presented here were prepared by a panel of experts nominated by the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV) in order to present the indications for treatment currently considered as effective and to summarize the evidence base for the use of IVIg.

These guidelines are intended to support informed therapeutic decision making on the use of IVIg for dermatologists.

The current guidelines represent consensual expert opinions and definitions on the use of IVIg reflecting current published evidence. The guidelines were prepared based on two rounds of evaluation of the previous guidelines (2011) with an individual update by each representative expert on the panel followed by a separate meeting of all panel members with discussion on the identified topics. The email-based evaluation period and the following expert panel meeting with discussion were coordinated and moderated by Professor Dr. med. A. Enk. An informal consensus was reached during the panel discussions; a structured formal consensus procedure was not applied.

The guidelines project did not receive financial support. The expert group did not receive financial incentives or reimbursement for the participation in the guidelines development. The summary of evidence was done independently from industrial interest.

A declaration of potential conflicts of interest (COI) adapted from the International Committee of Medical Journal Editors was required for the participation in the guidelines development. COIs were discussed. The expert group did not see any substantial conflicts of interest and there were no further comments or remarks. COI of each person involved in the guidelines development are presented in the appendix.

External reviewing was done according to EDF SOP for guidelines development over a period of four weeks, including the members of the EDF guidelines commission, the EADV Board and the UEMS (Union Européenne des Médecins Spécialistes). During the review period, the draft was piloted within the departments of the participating experts. Comments and necessary changes coming from the external review were being discussed among the authors. European guidelines are subject to national or regional adaptation with consideration of local circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated to the EDF will be responsible for the adaption and implementation of the guidelines on a national level.

Due to the increasing amount of publications, guidelines need to be continually updated to reflect the recent state of evidence. After December 31st, 2019 these guidelines will expire. Should important changes occur in the meantime, such as new available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guidelines will be outdated earlier. In these cases, an update issue of the guidelines is needed earlier. The EDF in cooperation with the current guidelines coordinator (Enk) will be responsible to initiate an update.

Conflict of interest

The Conflict of interest (COI) statements of all persons involved in the guidelines development are presented in the appendix.

Correspondence to

Prof. Dr. med. Alexander Enk
Department of Dermatology
Ruprecht-Karls-University Heidelberg

Im Neuenheimer Feld 440
69120 Heidelberg

E-Mail: alexander.enk@med.uni-heidelberg.de

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APPENDIX

Conflicts of interests

The Work Under Consideration for Publication					
		R.Eming Marburg	A. Enk Heidelberg	G. Fierlbeck Tübingen	L. French Zürich
1	Grant				
2	Consulting fee or honorarium				
3	Support for travel to meetings for the study or other purposes				
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like				
5	Payment for writing or reviewing the manuscript				
6	Provision of writing assistance, medicines, equipment, or administrative support				
7	Other				
*This means money that your institution received for your efforts on this study.					
Relevant financial activities outside the submitted work					
1	Board membership				
2	Consultancy		Biotest AG MSD Oncology Galderma Lab. Janssen-Cilag Abbvie		Novartis Galderma
3	Employment				
4	Expert testimony				
5	Grants/grants pending	Fresenius Medical Care			
6	Payment for lectures including service on speakers bureaus	Biotest	Bristol Myers-Squibb Roche Pharma		
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations				
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**				
13	Other (err on the side of full disclosure)				
*This means money that your institution received for your efforts. **For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.					
Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?				

The Work Under Consideration for Publication					
		G. Girolomoni Verona	E. Hadaschik Heidelberg	M. Hertl Marburg	S. Jolles Cardiff
1	Grant			Biotest Fresenius	CSL Behring Baxalta
2	Consulting fee or honorarium			GSK UCB Almirall	CSL Behring Baxalta Biotest
3	Support for travel to meetings for the study or other purposes			Fresenius	CSL Behring Baxalta
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like			GSK	UCB Pharma
5	Payment for writing or reviewing the manuscript				
6	Provision of writing assistance, medicines, equipment, or administrative support				
7	Other				
*This means money that your institution received for your efforts on this study.					
Relevant financial activities outside the submitted work					
1	Board membership				
2	Consultancy			Biogen Idec Biotest	Shire SOBI BPL NISCHR
3	Employment				
4	Expert testimony				
5	Grants/grants pending				SOBI Binding Site
6	Payment for lectures including service on speakers bureaus			Janssen-Cilag	
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations			Janssen-Cilag	
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**			AbbVie Janssen Cilag	
13	Other (err on the side of full disclosure)				
*This means money that your institution received for your efforts.					
**For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.					
Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?				

The Work Under Consideration for Publication						
		S. Karpati Budapest	K. Steinbrink Mainz	G. Stingl Wien	B. Volc-Platzer Wien	D. Zillikens Lübeck
1	Grant					Dompe Inc. Almirall Euroimmun Inc
2	Consulting fee or honorarium					Almirall Miltenyi UCB Inc. Biogen Dompe Roche Fresenius arGEN X Belg.
3	Support for travel to meetings for the study or other purposes					
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like					
5	Payment for writing or reviewing the manuscript					
6	Provision of writing assistance, medicines, equipment, or administrative support					
7	Other					

*This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work						
1	Board membership					
2	Consultancy		Affiris Bayer Healthcare Delenex Eli Lilly Merck Sharp&Dohme Novartis		Novartis	Euroimmun INc. Almirall UCB Fresenius arGEN X, Belg.
3	Employment					
4	Expert testimony					
5	Grants/grants pending	CSL Behring				Euroimmun Inc. Miltenyi Inc. Fresenius Inc. Biotest Inc. Dompe Inc. Almirall Biogen Roche
6	Payment for lectures including service on speakers bureaus		AbbVie Delenex DiaSorin Janssen-Cilag Merck Sharp & Dohme Novartis		Pelpharma Bayer Galderma MEDA Biotest CSL Behring	Biotest Fresenius Inc. Miltenyi Inc. Roche Pharma Inc.

7	Payment for manuscript preparation	
8	Patents (planned, pending or issued)	Euroimmun Inc.
9	Royalties	
10	Payment for development of educational presentations	
11	Stock/stock options	
12	Travel/accommodations/ meeting expenses unrelated to activities listed**	Fresenius Inc. Miltenyi Inc. AbbVie Inc. Roche Pharma UCB Inc. Biotest Biogen Janssen
13	Other (err on the side of full disclosure)	

*This means money that your institution received for your efforts.
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Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	