



# European Dermatology Forum

## Guidelines on the use of high-dose intravenous immunoglobulin in dermatology

Developed by the Guideline Subcommittee of the  
**European Dermatology Forum**

### *Subcommittee Members:*

Prof. Dr. A. Enk, Heidelberg (Germany)  
Prof. Dr. G. Fierlbeck, München (Germany)  
Prof. Dr. L. French, Zürich (Switzerland)  
Prof. Dr. G. Girolomoni, Verona (Italy)  
Prof. Dr. M. Hertl, Marburg (Germany)  
Prof. Dr. S. Jolles, Cardiff (United Kingdom)  
Prof. Dr. P. Joly, Rouen (France)  
Prof. Dr. S. Karpati, Budapest (Hungary)  
Prof. Dr. G. Messer, München (Germany)  
Prof. Dr. M. Meurer, Dresden (Germany)  
Prof. Dr. K. Steinbrink, Mainz (Germany)  
Prof. Dr. G. Stingl, Vienna (Austria)  
Prof. Dr. B. Volc-Platzer, Vienna (Austria)  
Prof. Dr. D. Zillikens, Lübeck (Germany)

### *Members of EDF Guideline Committee:*

Prof. Dr. Werner Aberer, Graz (Austria)  
Prof. Dr. Martine Bagot, Créteil (France)  
Prof. Dr. Lasse Braathen, Bern (Switzerland)  
Prof. Dr. Sergio Chimenti, Rome (Italy)  
Prof. Dr. José Luis Diaz-Perez, Bilbao (Spain)  
Prof. Dr. Vladimír Hegyi, Bratislava (Slovak Republic)  
Prof. Dr. Lajos Kemény, Szeged (Hungary)  
Prof. Dr. Hans Christian Korting, Munich (Germany)  
Prof. Dr. Gillian Murphy, Dublin (Ireland)  
Prof. Dr. Martino Neumann, Rotterdam (The Netherlands)  
Prof. Dr. Tony Ormerod, Aberdeen (UK)  
Prof. Dr. Annamari Ranki, Helsinki (Finland)  
Prof. Dr. Fenella Wojnarowska, Oxford (UK)

### *Chairman of EDF Guideline Committee:*

Prof. Dr. Wolfram Sterry, Berlin (Germany)

Expiry date: 8/2011

---

*List of conflicts of interest:*

Prof. Dr. Alexander Enk, Heidelber (Germany)	received a grant support of Biotest
Prof. Dr. Detlef Zillikens, Lübeck (Germany)	received a support of Biotest
Prof. Dr. Stephen Jolles, Cardiffe (United Kingdom)	is on the Baxter Advisory Board is chief investigator for a study with CSL Behring received a support of CSL Behring Baxter, BPL, Octapharma and Grifols is on the Baxter Scientific Board
Prof. Dr. Gerald Messer	no conflict declared
Prof. Dr. Lars French	no conflict declared
Prof. Dr. Michael Hertl	no conflict declared
Prof. Dr. Giampiero Girolomini	no conflict declared
Prof. Dr. Sarolta Kárpáti	no conflict declared
Prof. Dr. Kerstin Steinbrink	no conflict declared
Prof. Dr. Gerhard Fierlbeck	no answer
Prof. Dr. Pascal Joly	no answer
Prof. Dr. Michael Meurer	no answer
Prof. Dr. Beatrix Volc-Platzer	no answer
Prof. Dr. Georg Stingl	no answer

The treatment of severe dermatological autoimmune diseases and toxic epidermal necrolysis 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 very severe disease courses, the use of immunoglobulin is not generally based on experiences from controlled and randomized trials that are usually required for the practice of evidence-based medicine. Owing to the rarity of indications for the use of IVIg, it is also unlikely that such studies will be available in the foreseeable future. Because the high costs of IVIg treatment also limit its first-line use, no clear guidelines have existed so far on its use in dermatological conditions. This manuscript represents the consensus of a European Guidelines working group of the EDF and EADV which is intended to serve as a decision-making tool for the use of IVIg in dermatological conditions.

### **Introduction:**

Immunoglobulin preparations are obtained from the pooled plasma of between 3,000 and approximately 10,000 individual donors. The purpose of this pooling is to provide the entire array of antibodies sometimes referred to as a species repertoire and also naturally occurring auto-antibodies as found in normal serum to be represented using the preparation obtained, although this large number of donors in the pool naturally increases the risk of diluting any rare specific activity.

Another problem associated with the large number of donors is the risk of transmission of latent infections. 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 writing and regular updating of these guidelines is governed by the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMA) and the Monograph in the European Pharmacopoeia.

These guidelines and recommendations regulate 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. These regulatory bodies carry out testing and dictate 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 infections or chronic

---

diseases. All plasma donation 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 “lookback” 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 retrospectively 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 3 weeks. The  $F_C$  region of the IgG permits interactions and signal transductions by  $F_C$  gamma receptors on numerous immune cells. The mechanism of action of immunoglobulins is complex and has not been elucidated completely in vivo. There are numerous theories which are supported to a greater or lesser degree by in vitro data, but no definitive in vivo evidence of the main mechanism of action. The role played by  $F_C$  receptors in relation to the activity of IVIg has recently become the primary focus of attention. Immunoglobulins have been used for more than 25 years in the treatment of diseases associated with primary and secondary immune deficiency. In dermatology, IVIg is used mainly in the treatment of autoimmune diseases and toxic epidermal necrolysis. 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 European guidelines presented here were drawn up by a panel of experts in order to present the indications for treatment currently considered as effective and to summarise the evidence base for the use of IVIG to inform therapeutic decision making.

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

1. Which diseases are indications for IVIg?
2. Is the use of IVIg indicated as first- or second-line treatment?
3. What is the initial duration of treatment?
4. Interval between IVIg infusion cycles?
5. Dosing of immunoglobulin therapy?
6. Duration of treatment per IVIg cycle?
7. Are methods available for assessing therapeutic efficacy?
8. Is long-term treatment advisable?

### **Dermatomyositis:**

Dermatomyositis is the condition in which the highest level of evidence exists for treatment with IVIg. There are numerous individual case reports and small case series as well as a double-blind, placebo-controlled crossover study which demonstrate the efficacy of IVIg.

The following criteria were drawn up by the European Guidelines working group:

**1. Indications:** All severe forms of dermatomyositis, inclusion body myositis or polymyositis represent indications for the use of IVIg. This applies to what is referred to as idiopathic, paraneoplastic or juvenile form respectively.

**2. Timing of treatment:** The comparatively good data available for these disease forms justifies the early use of IVIg in dermatomyositis. In patients with fulminant progressive courses, 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 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. IVIg monotherapy has generally not proven effective. For this reason, the use of IVIg

---

therapy should not be delayed for too long so that a sufficient bone marrow reserve is available for the concomitant immunosuppressive therapy.

**3. Initial duration of treatment:** Initial treatment should be carried out over a period of 6 months in order to determine the efficacy of treatment with IVIg. Therapeutic efficacy should have been achieved after 6 treatment cycles, however, or else the IVIg treatment should be discontinued. After 12 treatment cycles, a washout period should be attempted, it being possible to increase the interval between infusions to a maximum of 6 weeks beforehand. In the event of recurrences, treatment can be resumed at any time.

**4. Interval between infusions:** Initially, adjuvant IVIg therapy should be administered every 4 weeks. If a good clinical response is achieved, the interval can be increased gradually to a maximum of 6 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 mainly with a dose of 2 g per kg body weight per treatment cycle. Because there is no clear evidence of efficacy with lower doses, strict adherence to the aforementioned dose recommendations is required in these serious diseases.

**6. Period of IVIg administration:** Administration of the immunoglobulin should be spread over 2-5 consecutive days. Tolerability is generally better with greater dose fractionation. In patients with cardiac or renal impairment, immunoglobulin preparations should be administered over a longer period of time. If the treatment is initially well tolerated, this 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. Auto-antibody titers, on the other hand, do not reflect the response to treatment. Creatine kinase and muscle aldolase levels also generally return to normal rapidly under immunosuppressive therapy. This prohibits their use as indicators of efficacy. MRI or ultrasonography of the proximal muscle groups are important for the initial diagnosis and specific muscle biopsy, but are unsuitable for close monitoring. The criteria for evaluating the clinical response must therefore be 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 under IVIg therapy. Based on experience, a response can be detected from the 2nd treatment cycle, mainly by the patient (especially on the basis of the improvement in muscle strength) but

also by the doctor. Tapering the concomitant medication too rapidly should be avoided, however. Between 3 and 4 treatment cycles are often required before a significant improvement in symptoms is seen.

**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.

Evidences for systemic therapies in dermatomyositis:

IVIg	level of evidence I-b	grade of recommendation A
Systemic steroids	level of evidence III	grade of recommendation A
Others	level of evidence IV	grade of recommendation B

(Hierarchy of evidence corresponding to the recommendation of the US Agency for Health Research and Quality AHRQ)

**Autoimmune blistering diseases:**

Autoimmune diseases are autoantibody-mediated disorders, the autoantigens of which are largely known and have been molecularly characterized. Autoimmune blistering diseases are generally treated only by dermatologists 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 diseases which are refractory to therapy represent an indication for the use of IVIg (level of evidence III, recommendation grade B). The experiences are particularly good in pemphigus vulgaris (level of evidence III, grade of recommendation B), pemphigus foliaceus (level of evidence III, grade of recommendation B), mucous membrane pemphigoid (level of evidence III, grade of recommendation B) and epidermolysis bullosa acquisita (level of evidence IV, grade of recommendation C). However, the use of immunoglobulin may also be indicated in severe forms of bullous pemphigoid (level of evidence III, grade of recommendation B), linear IgA disease (level of evidence IV, grade of recommendation C), IgA pemphigus or paraneoplastic pemphigus (level of evidence IV, grade of recommendation C).

**2. Timing of treatment:** For evidence based and also economic reasons, the use of IVIg cannot be recommended as a first-line treatment. However, contraindications to standard immunosuppressive therapy (aseptic bone necrosis, poorly controlled diabetes or even advanced

---

osteoporosis and cataracts) may in isolated cases justify the use of IVIg as a first-line treatment. Consequently, immunoglobulins should only be used as a second-line treatment following sufficient combination therapy with steroids (e.g. prednisolone 2 mg per kg body weight per day) and another immunosuppressive agent (e.g. mycophenolate mofetil). Here again, IVIg is an adjuvant therapy which must be administered while continuing the conventional immunosuppressive therapy. 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 an adequate bone marrow reserve. Monotherapy with immunoglobulin is not generally recommended.

**3. Initial duration of treatment:** Treatment should be administered initially for a period of between 3 and 6 months in order to test the efficacy of the IVIg in the individual case. Some patients do not show a definitive sustained response until they have undergone 6 cycles of treatment. If there should be no response to treatment after 6 cycles of treatment, discontinuation of the IVIg treatment is advisable.

**4. Interval between infusions:** Adjuvant therapy with IVIg should be administered every 4 weeks initially. If the clinical response is good, the interval between infusions can be increased gradually to a maximum of 6 weeks. Longer intervals are not recommended because of the half-life of IVIg.

**5. Dosing:** As already mentioned above, the only positive experiences available at present are with 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.

**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.

**7. Evaluation of treatment efficacy:** Besides the clinical picture, serological parameters can also be 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. The now well established enzyme immunoassays can be used as serological parameters for assessing the efficacy of treatment (particularly for pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid and mucous membrane pemphigoid). Indirect immunofluorescence testing can also be used as an

indicator of response. Because the titre patterns do not in all cases reflect the clinical picture, this method should be used only in a supplementary manner.

**8. Long-term therapy:** Long-term therapy with IVIg is recommended only in rare cases. An exception to this are cases in which disease recurrence occurs after withdrawal of IVIg therapy and no other treatment options exist. Regular washout periods should be attempted.

### **Vasculitic syndromes:**

Vasculitic syndromes are systemic inflammatory conditions which can affect the blood vessels of various organ systems. 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 are therefore proposed:

**1. Indication:** Only in Kawasaki's disease is IVIg the treatment of first choice (level of evidence I a, recommendation grade A). Primary treatment generally consists of high-dose corticosteroids with the aid of additional immunosuppressive agents such as cyclophosphamide or others. The use of these often very aggressive immunosuppressive regimens is often associated with severe side effects, and recurrences often occur on withdrawal or dose reduction. In patients who do not respond to standard therapy or those with a particularly fulminant progressive disease form with multiple complications and severe side effects, IVIg therapy should be included as a first-line treatment option. All forms of vasculitis can therefore present possible indications for IVIg. Particularly positive results have been achieved in primary vasculitis, e.g. Wegener's granulomatosis (level of evidence I a, recommendation grade B), polyarteritis nodosa (level of evidence grade IV, recommendation grade D), IgA-associated vasculitis (level of evidence class III, recommendation grade D), Churg-Strauss disease (level of evidence class I, recommendation grade B), microscopic polyangiitis (level of evidence grade I a, recommendation grade B), and in secondary autoimmune vasculitis (level of evidence class III, grade of recommendation grade D). Good results have also been achieved in patients with anti-phospholipid antibody syndrome (level of evidence in obstetric use II, recommendation grade C; in catastrophic APS level of evidence IV, recommendation grade C).

**2. Timing of treatment:** Only for Kawasaki's syndrome is IVIg authorized 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

---

defects in conditions such as haemorrhagic 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.

**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 6 weeks. Any further extension of interval between infusions is not useful.

**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) 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.

**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, for example. In Wegener's granulomatosis, the c-ANCA titre pattern can be also used as one of the indicators.

**8. Long-term therapy:** Long-term therapy with IVIg is recommended only in exceptional cases.

### **Lupus erythematoses, and other collagen vascular diseases:**

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

**1. Indication:** In principle, all severe forms of autoimmune diseases can represent an indication for attempted treatment with IVIg if no other treatment options are available. Its use in systemic lupus erythematosus (evidence level III), especially in lupus nephritis (Toubi et al, 2006), is considered effective. Less clear are the data in patients with scleroderma, in which no clear recommendation can be expressed (Levy et al, 2004).

**2. Timing of treatment:** The use of IVIg is not generally a first-line treatment option. Previous combination treatment with steroids and another immunosuppressive associated with a poor response or severe complications is considered a condition for the use of IVIg. Again, however, the use of IVIg should not be delayed for too long in conditions such as lupus nephritis if bone marrow damage is to be avoided which will be detrimental to subsequent adjuvant IVIg therapy. Here too, treatment should be given in combination with adequate immunosuppressive therapy.

**3. Initial duration of treatment:** As with the aforementioned conditions, use is initially recommended over a period of 6 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 4 weeks. The interval between the individual bolus infusions can then be increased gradually to 6 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 these conditions is with the standard dose of 2 g per kg body weight. This should be adopted as the standard recommendation.

**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 generally be increased to 5 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, here again 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 auto-antibodies 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.

---

## **Toxic epidermal necrolysis:**

Toxic epidermal necrolysis represents a life-threatening side effect of drugs. The condition is associated with FAS-mediated apoptosis of the epidermal keratinocytes. Because of the 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 numerous studies, the early administration of IVIg in toxic epidermal necrolysis has proven potentially life-saving (evidence level IIIb, recommendation grade C) (Viard et al, Mittmann, N et al). Although the mechanism of action is unclear, the early administration of high-dose immunoglobulin is considered to be the recommended treatment where there is a confirmed diagnosis and in severe forms of toxic epidermal necrolysis in the absence of any therapeutic alternative.

**2. Timing of treatment:** Unlike in the aforementioned conditions, IVIg must be administered as soon as possible after confirmation of the diagnosis. IVIg treatment can then be administered as monotherapy in addition to 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 other autoimmune diseases. A total dose of 3 g per kg body weight is generally recommended. Fractionated administration (over 3-5 days) is required, particularly in the case of renal impairment in these patients who are already very vulnerable.

**5. Evaluation of treatment efficacy:** The onset of re-epithelialization is the best clinical parameter for evaluating treatment efficacy. The contribution of IVIg to the healing process is naturally 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 the dermatological literature. Some of the more frequent entities will be mentioned here, although a conclusive assessment is not possible at present.

#### **Atopic dermatitis (evidence level III):**

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 treatment (Paul et al, 2002; Jolles & Hughes, 2006).

#### **Autoimmune urticaria (evidence level III):**

The use of immunoglobulin can also be considered as a last resort in severe cases of autoimmunologically mediated urticaria. Only isolated 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 (Jolles & Hughes, 2006). A conclusive assessment of these reports is not possible at the present time.

#### **Scleromyxoedema (evidence level III):**

As most of the reports on the treatment of scleromyxoedema with IVIg show improvement or healing of this disease, IVIg should be considered treatment of choice in refractory cases, although this recommendation is solely based on small case series.

Successful case reports exist. However final conclusions are not possible due to the lack of larger studies.

#### **Pyoderma gangraenosum (evidence level III-IV):**

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

### **Summary:**

The treatment recommendations presented for the use of IVIg in dermatology highlight the high status of IVIg therapy in numerous defined dermatological autoimmune diseases and in toxic epidermal necrolysis. The high value of IVIg therapy in diseases which are otherwise refractory to treatment is undisputed. A clear case therefore exists for making a treatment recommendation

---

such as described above for the conditions mentioned. Because the mechanism of action of IVIG in vivo is still unclear, however, further efforts should be made to come to standard therapies for the affected patient groups. This would enable even larger case series conducted by different therapists at different sites to be evaluated. Orientation towards the guideline recommendations laid down here should create a basis for this. The implementation of this EU guideline in general practice means that the use of IVIg in dermatology will be optimized throughout Europe.

## Table 1

### **Indications for the use of IVIg**

- Severe forms of dermatomyositis, inclusion body myositis, polymyositis
- Toxic epidermal necrolysis
- Severe forms of autoimmune blistering disease
- Severe systemic vasculitic syndromes
- Severe forms of lupus erythematoses

### **Less obvious indications**

- Atopic dermatitis
  - Autoimmune urticaria
  - Scleromyxoedema
  - Severe forms of collagen vascular diseases
-

## Table 2

### **Recommended dosage regimens**

<b>Dosage:</b>	total 2 g/kg body weight *, divided into 2-5 infusions
<b>Treatment interval:</b>	initially every 4 weeks / after 6 months gradually increase to 6-week intervals **
<b>Long-term therapy:</b>	In individual cases

\*3 g/kg body weight in TEN

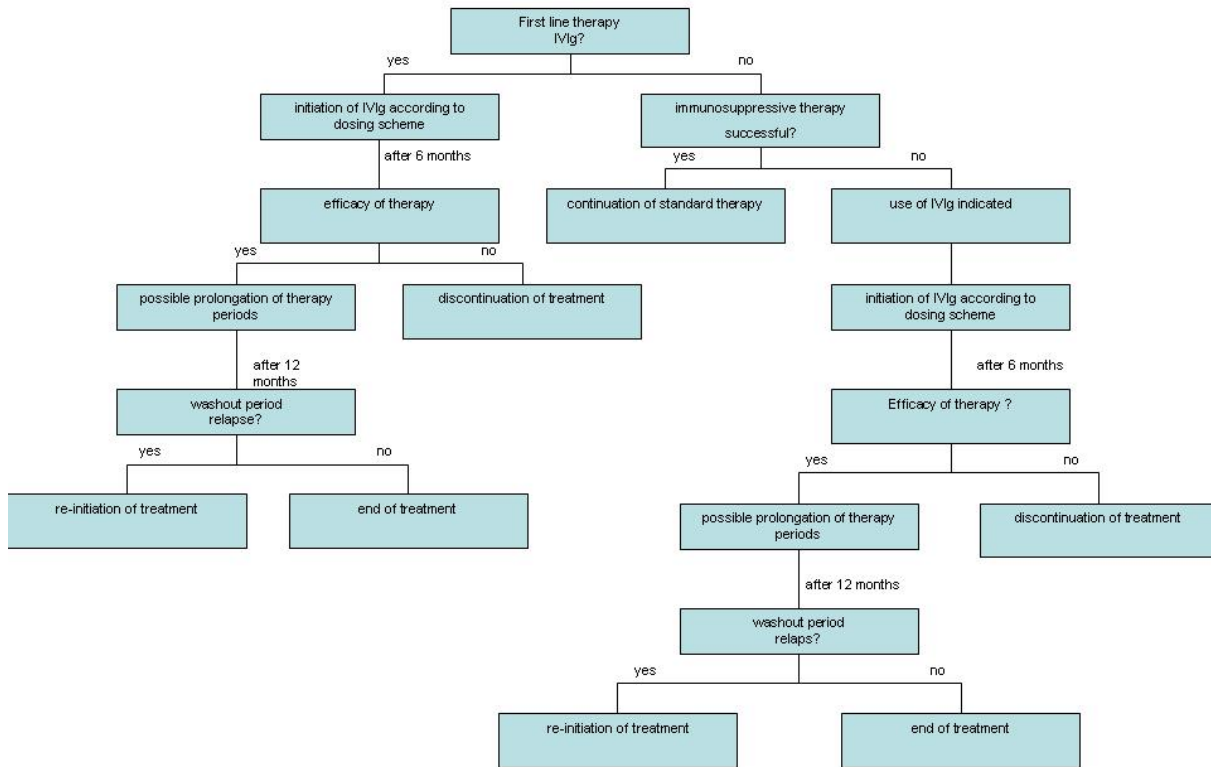
\*\* Only 1 cycle in Kawasaki's disease and TEN

## Literature:

1. Amato AA, Barohn RJ, Jackson CE, Pappert EJ, Sahenk Z, Kissel JT. Inclusion body myositis: treatment with intravenous immunoglobulin. *Neurology* 1994;44:1516-8.
  2. Aries PM, Hellmich B, Gross WL. Intravenous immunoglobulin therapy in vasculitis. *Clin Rev All Immunol*; 2005; 29:237-245
  3. Cherin P, Piette JC, Wechsler B, Bletry O, Ziza JM, Laraki R, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. *J Rheumatol* 1994;21:1092-7.
  4. Choy EHS, Hoogendijk JE, Lecky B, Winer JB. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Art. No.:* CD003643.
  5. Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. *Neurology*. 2001;56:323-7.
  6. Dalakas MC. Update on the use of intravenous immune globulin in the treatment of patients with inflammatory muscle disease. *J Clin Immunol* 1995;15:70S-5S.
  7. Enk A, Hertl M, Messer G, Meurer M, Rentz E, Zillikens D. The use of high dose intravenous immunoglobulins in dermatology. *J Dtsch Dermatol Ges*. 2003 Mar;1(3):183-90. German.
  8. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, Hunzicker T, Saurat JH, Tschopp J, French L. Inhibition of TEN by blockade of CD95 with human IVIg. *Science* 1998 Oct; 282: 490-493
  9. *Mittmann N, Chan BC, Knowles S, Shear NH. IVIg for the treatment of toxic epidermal necrolysis. Skin therapy Lett*. 2007 Feb; 12 (1): 7-9.
  10. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. *Arch Dermatol*. 1998 Jan;134(1):80-6.
  11. Jolles S, Hughes J. Use of IGIV in the treatment of atopic dermatitis, urticaria, scleromyxedema, pyoderma gangrenosum, psoriasis, and pretibial myxedema. *Int Immunopharmacol*. 2006 Apr;6(4):579-91. 2005 Dec 13. Review.
  12. Karim A, Lawlor F, Black MM. Successful treatment of scleromyxoedema with high dose intravenous immunoglobulin. *Clin Exp Dermatol*. 2004 May;29(3):317-8.
  13. Körber A, Franckson T, Grabbe S, Dissemmond J. (2007) Successful therapy of scleromyxoedema Arndt-Gottron with low-dose intravenous immunoglobulin. *Journal of the European Academy of Dermatology and Venereology* 21:4, 553–554
  14. Kukova G, Bruch-Gerharz D, Gensch K, Ruzicka T, Reifenberger J. (2006) Skleromyxödem. *Der Hautarzt* 57:4, 326
  15. Levy Y, George J, Fabbrizzi F, Rotman P, Paz Y, Shoenfeld Y. Marked improvement of Churg-Strauss vasculitis with intravenous gammaglobulins. *Southern Medical Journal*. 1999; 92(4):412-414
  16. Levy Y, Langevitz P, Nacci F, Righi A, Conforti L, Generini S, Shoenfeld Y. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open label study. *Arthritis Rheum*. 1005-7, 2004
  17. Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol*. 2002 Sep;147(3):518-22.
  18. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol*. 2007 Feb;56(2):181-200.
-

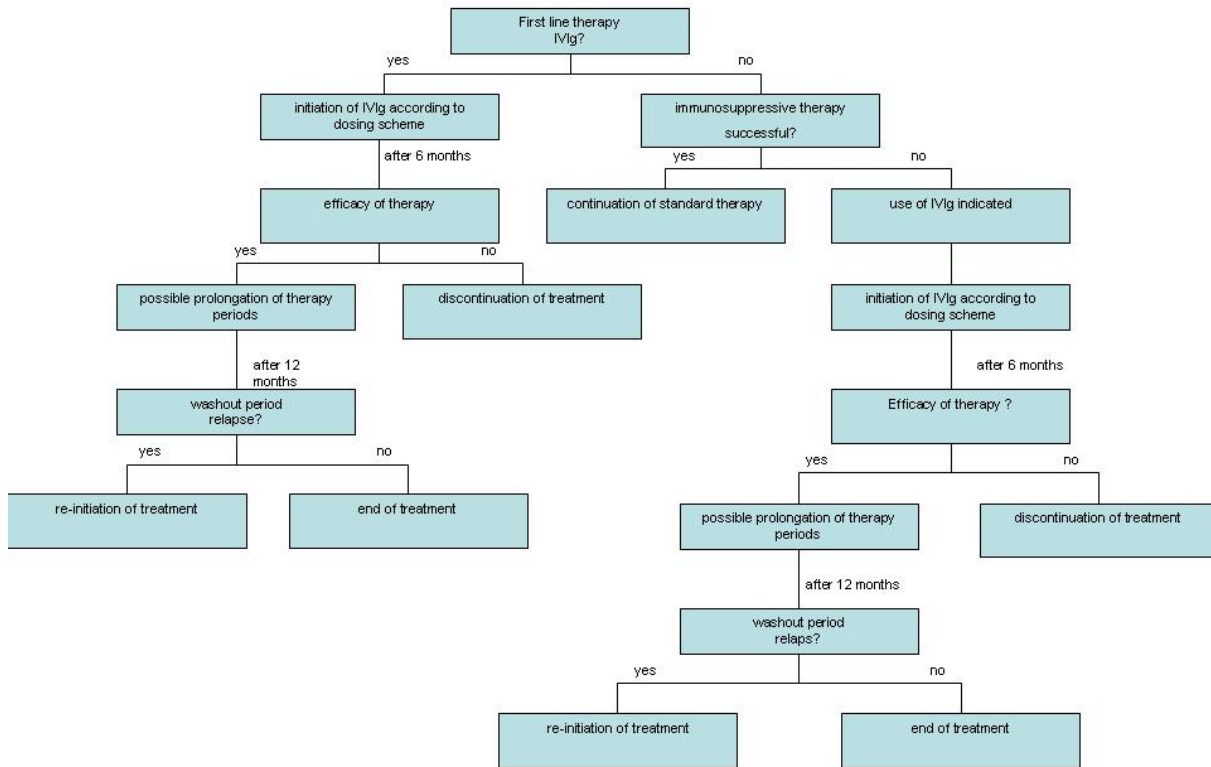
19. Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm Venereol.* 87:206-18, 2007
20. Richter C, Schnabel A, Csernok E, De Groot K, Reinhold-Keller E, Gross WL. Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin. *Clin Exp Immunol.* 1995; 101:2-7
21. Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis-four year review of nine cases. *Arch Dis Child* 1995;72:25-8.
22. Schanz S, Ulmer A, Fierlbeck G. Intravenous immunoglobulin in livedo vasculitis: A new treatment option? *A Am Acad Dermatol.* 2003; 49(3):555-556
23. Shoenfeld Y, Katz U. IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients. *Autoimmunity.* 2005; 38(2):123-137
24. Topf S, Simon M jr., Schell H, Lüftl M. (2006) Deutliche Besserung eines Skleromyxödem Arndt-Gottron durch hoch dosierte intravenöse Immunglobuline. *Der Hautarzt*
25. Toubi E, Kessel A, Shoenfeld Y. High dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. *Hum. Immunol* (2005) 66:395-402

## Decision Tree IVIg severe autoimmune diseases





## Decision Tree IVIg severe autoimmune diseases



**SOP for creation of European Dermatology Guidelines**

Step	Responsible	Task	Months duration
1	EDF Guidelines Committee (EDF-GC)	Decision of topic of specific guideline	∅
2	EDF Board	Confirmation of the choice and level of guideline (S1, S2 or S3) plus suggestion to the Guideline Committee of potential chairmen and subcommittee members.	0,5
3	EDF Guidelines Committee	Foundation of subcommittee for specific guidelines. Nomination of EDF members (50 %) as well as identification of possible EADV members (25 % of members for the subcommittee) who could work within the subcommittee. Chairman of EDF guideline committee asks EADV president for approval. Finally nomination of a chairperson of the subcommittee by the group.	at EDF Meeting
4	EDF-GSubC	Development of a business plan (see attachment)	1
5	EDF Board	Confirmation of business plan and signature of the contract for financial support of guideline	1
6	EDF Guidelines Subcommittee (EDF-GSubC)	Identify all existing guidelines for the specific guideline (active process: literature survey plus contact to Dermatological Societies)	1
7	EDF Guidelines Subcommittee	Select the guidelines with highest quality. Criteria for selection: 1. Availability of strength of evidence 2. Availability of strength of recommendation 3. Evidence of mechanics of literature review (adhere to the recommendations of the Cochrane collaboration. These standards should assure high quality for the systematic literature search as well as for the critical appraisal of the papers. For further information see <a href="http://www.cochrane.org/crgprocedures/chapter4/1.htm">http://www.cochrane.org/crgprocedures/chapter4/1.htm</a> and documents available at EDF Guidelines Secretariat (Mrs. Janine Schweiger, <a href="mailto:janine.schweiger@charite.de">janine.schweiger@charite.de</a> )	1
8	EDF Guidelines Subcommittee	Identification/nomination of additional 50 % EDF members for the EDF-GSubC from amongst the authors of the best guidelines	0,5
9	Chairperson of Subcommittee	Consider involvement of other disciplines and patients' organisations	1
10	EDF Guidelines Subcommittee	Meet 1. to decide the author of the first draft (normally the chairperson of the subcommittee) and to discuss the present guidelines, their strengths and weaknesses 2. 6 months later to discuss the draft (consensus conference)	6
11	Chairperson of Subcommittee	Circulate the guideline draft to national dermatological societies for comments	2
12	Guidelines Subcommittee	Circulate final version for approval among members of the guideline subcommittee	1
13	Chairperson of Subcommittee	Deliver final version for comments to EDF guideline committee chairperson, who forwards it to EADV Board and to UEMS	2
14	EDF Guidelines Committee	Review and comment guideline	1
15	EDF Guidelines Committee chairperson	Send guideline for official approval to UEMS (formal approval)	2
16	EDF secretary	Distribute guideline for in advance information to EDF members and National Dermatological Societies	1
17	EDF	Publication 1. on EDF homepage 2. in European dermatological journals 3. If publication in other national and international journals is requested by the respective society, this will be encouraged by the EDF	6