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**Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management**

**Abbreviated title**: Hypersensitivity reactions to intravenous iron

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Abbreviations

ACE (Angiotensin Converting Enzyme)

ADRs (Adverse drug reactions)

API (active pharmaceutical ingredient)

C (Complement)

CARPA (Complement activation-related pseudoallergy)

CHMP (Committee for Medicinal Products for Human Use)

EMA (European Medicinal Agency)

HMW-ID (High molecular weight iron dextran)

HSRs (Hypersensitivity reactions)

ID (Intravenous dextran)

IV (Intravenous)

IV-iron (Intravenous iron)

L-Dox (Doxorubicin-HCl Liposome (Doxil = Caelyx)

LMW-ID (Low molecular weight iron dextran)

LRP (low-risk protocol

Mab (Monoclonal antibody

WAO (World Allergy Organisation)

Abstract

Intravenous (IV) iron therapy is widely used in iron deficiency anemias when oral iron is not tolerated or ineffective. Administration of IV iron is considered a safe procedure, but severe hypersensitivity reactions (HSRs) can occur at a very low frequency. Recently, new guidelines have been published by the European Medicines Agency (EMA) with the intention of making IV-iron therapy safer; however, the current protocols are still non-specific, non-evidence-based empiric measures which neglect the fact that the majority of IV-iron reactions are not Ig-E-mediated anaphylactic reactions. The field would benefit from new specific and effective methods for the prevention and treatment of these HSRs, and the main goal of this review was to highlight a possible new approach based on the assumption that IV-iron reactions represent complement (C) activation-related pseudo allergy (CARPA), at least in part. The review compares the features of IV-iron reactions to those of immune and non-immune HSRs caused by a variety of other infused drugs and thus make indirect inferences on IV-iron reactions. The process of comparison highlights many unresolved issues in allergy research, such as the unsettled terminology, multiple redundant classifications and a lack of validated animal models and *lege artis* clinical studies. Facts and arguments are listed in support of the involvement of CARPA in IV-iron reactions, and the review addresses the mechanism of low reactogenic administration protocols (LRPs) based on slow infusion. It is suggested that consideration of CARPA and the use of LRPs might lead to useful new additions to the management of high-risk IV-iron patients.

Keywords:

* iron deficiency
* drug allergy
* pseudoallergy
* anaphylaxis
* complement
* anaphylatoxin
* CARPA
* anemia
* chronic kidney disease
* dialysis

Introduction

It has been reported that roughly 25 % of all adverse drug reactions (ADRs) are hypersensitivity reactions (HSRs), affecting up to some half-million patients in the USA every year (Lazarou *et al.*, 1998). Such reactions can be caused by almost all types of drugs, irrespective of their chemical composition, complexity or route of administration. Because of recent public concern about the HSRs caused by one of such reactogenic drugs, namely intravenous iron (IV-iron) compounds (EMA-CHMP, 2013), this review focuses on the HSRs caused by these preparations.

Parenteral iron (IV-iron) has become an important treatment for iron deficiency anemia in a wide range of therapeutic areas, when oral iron is inappropriate, ineffective or not tolerated. A recent safety review performed by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA-CHMP) concluded that all available IV-iron preparations on the European market have a positive risk-benefit ratio and low risk of causing HSRs. In order to minimize the risk of life threatening reactions new recommendations were introduced for all health care professionals who provide treatment with IV-iron. The document (EMA-CHMP, 2013) calls for changes in the practice of IV-iron infusions (Table 1) and for uniform reporting of HSRs (Ring and Mesmer, 1977; Ring *et al,* 2010).

Table 1. New recommendations by the EMA’s Committee for Medicinal Products for Human Use (CHMP) to manage risk of allergic reactions with IV-iron (EMA-CHMP, 2013).

However, the field would also benefit from scientific evidence-based introduction of more specific and effective measures than the currently applied common empiric ones. To achieve this, the mechanisms of IV-iron reactions should be better understood, and this challenge represents the main thrust of the present review. Our approach is to highlight the similarities and differences among iron- and other IV drug-induced HSRs that might give clues regarding the mechanisms, and, hence make possible new methods of prevention and treatment of IV-iron reactions. The comparison focuses on the symptoms of reactions categorized by their various properties. The process of comparison entails addressing some critical unsolved issues in the field, such as the incoherent terminology and lack of credible clinical data. A summary of current premedication and treatment options alludes to the inappropriateness of using antihistamines, since they mimic some of the features of HSRs, and provides rationale for the testing of low reactogenic administration protocols (LRPs), such as low-dose slow priming followed by slow dose escalation. One particular new perspective outlined for the first time in this review is the possible causal role of complement (C) activation in IV-iron reactions, a proposal which has both conceptual and therapeutic implications.

Features of HSRs to IV-iron versus those to other IV drugs

Fig 1 lists the symptoms and various features of HSRs caused by IV drugs, including IV-iron, by which the symptoms have been categorized: organ systems affected, severity, kinetics, prevalence, duration, mechanism and tolerance induction. Changes of the variables in these categories depend on the reactogenicity of the implicated drugs, the method of their administration and the patient’s sensitivity. A closer analysis of these variables reveals both similarities and major differences between the symptoms of reactions to IV-iron and to other IV drugs, as detailed below.



Fig 1. Hypersensitivity reactions and their different classifications: these relate to administration of any IV agent and are not specific to IV iron.

The *symptoms and their organ expression* do not seem to be different between IV-iron and other drugs, at least on the basis that almost all listed symptoms and all mentioned organ systems have been cited for HSRs to both IV-iron and non-iron drugs. Nevertheless, because the active pharmaceutical ingredients (API) usually have an impact on the physicochemical features of the drug, and, hence, on its immune reactivity, it is not impossible that a head-to-head comparison would reveal specific effects of iron on HSR symptoms. At this time, however, we are not aware of such quantitative data in the literature.

For the description of the *severity of symptoms*, the best known classification of HSRs was described by Ring and Messmer (Ring & Mesmer, 1977; Ring *et al,* 2010), who graded the symptoms to categories I-IV. This classification, which should not be confused with Gell and Coombs’ Type I-IV HSRs, which was recommended by the EMA (EMA, 2012) for ADR reporting, despite the existence of a simpler (Brown, 2004) and a more recent symptom-based grading systems (Mayer & Young, 2006). Irrespective of how HSRs are quantified, from mild to severe, life-threatening reactions can occur with either IV-iron formulation or other IV drugs. Severity does not differentiate between iron and non-iron reactions. Likewise, iron and non-iron HSRs can be acute, short, delayed and extended. Thus the *kinetics* and *duration of symptoms* are no distinguishing features.

*Prevalence* is the feature of HSRs that does radically differ between reactogenic drugs. When expressed as the percentage of patients displaying HSRs among all those treated, the range spans 5 orders of magnitude (0.001-70%). To enable the comparison of prevalence statistics within such wide limits, we propose clustering the % values into five groups (very high, high, moderate, low and very low) with numeric ranges coinciding with the orders of magnitude in the 10-3-102 range (3rd column in Fig. 1).

Table 2 categorizes the main drug types according to HSR prevalence. It turns out from the compilation that the highest rate of HSRs occur with certain monoclonal antibodies (mAbs), liposomal drugs and anticancer agents (taxanes) which are delivered in micellar solvents, such as Cremophor EL. The frequency of HSRs to penicillin, the textbook example of drug-induced allergic reactions, falls at the moderate/high borderline (1%). On the other hand the prevalence of HSRs to different IV-iron preparations is very low, a feature shared only with the safest radiocontrast agents (Table 2). In fact, the vast majority of IV-iron administrations in clinical practice occur with no or minor adverse events. The heightened public and regulatory concern about these reactions may therefore be considered as paradoxical.

Despite the very low prevalenceof IV-iron reactions, minor but significant differences between the risk rates might have major clinical implications Analyses of commercial and public databases (e.g., post-marketing surveillance data, voluntary submission of ADR-reports) have led some authors to claim differences in the safety profiles of currently available IV-iron products (Chertow *et al.*, 2004; Bailie *et al.*, 2005; Chertow *et al.*, 2006; Bailie *et al.*, 2011; Bailie, 2012; Bailie *et al.*, 2012). These reports were recently challenged by the mentioned EMA document (EMA-CHMP, 2013) and a recent review by Bircher and Auerbach (Bircher *et al.*, 2014) that concluded that insufficient reliable data are available to support this conclusion. There are many reasons for this uncertainty, such as the confusing terminology and classification of HSRs, under-reporting or differential reporting of IV-iron reactions, absence of brand names and a lack of accurate or uniform denominator information (i.e., whether the HSR-rate is given per infusion, per patient, per time or per all ADRs) (Wysowski *et al.* 2010). Moreover randomized clinical trials are not powered to compare very rare clinical events (Black, 1996). Critchly *et al.* (2007) concluded that a study to compare the event rate for two IV-iron compounds would need about 6600 patients to achieve the necessary statistical power. Nonetheless, a relatively higher rate and generally more severe HSRs were observed with high molecular weight (HMW) iron-dextran compared to the low (LMW) formulation (Fletes *et al.*, 2001, Chertow *et al*., 2004). Since that time, both HMW-dextrans (Imferon®, Dexferrum®) have been removed from the market by the marketing authorisation holders in USA. The problems with the terminology and classification of HSRs will be discussed in more detail below.

Table 2. Frequency of HSRs\* in patients treated IV with different reactogenic drugs

|  |  |  |
| --- | --- | --- |
| **Reaction****rate** | **Drugs** | **Drug Type** |
| Very highP > 10 % | Rituximab, Infliximab | mAb |
| L-Dox (Caelyx), Ambisome | Liposome-encapsulated |
| Taxanes (paclitaxel, docetaxel), platinum | micellarized anticancer |
| High1% < P <10 % | Natalizumab, Cetuximab, Trastuzumab, Panitumumab, Gentuzumab | mAb |
| Amphotec, Myocet, Amphocyl, DaunoXome, Abelcet, Visudyne | Liposome |
| Penicillin | Antibiotic |
| Platinum compounds (Cisplatin, Carboplatin), | Anticancer drugs |
| Moderate0.1 < P % <1 | OmalizumabAlemtuzumabTrastuzumab | Monoclonal antibodies (mAbs) |
| Cephalosporins/carbapenems, aztreonam, imipenem | antibiotics |
| Iodinated contrast agents (Ioxaglate, Iohexol, Iopamidol, Ioversol, Iopromide, Ioxilan) | radiocontrast agents |
| low0.01 < P % <0.1 | Bevacizumab | mAb |
| Epipodophyllotoxins (teniposide, etoposide), Asparaginase, Procarbazine, Doxorubicin, 6-mercaptopurine | anticancer drugs |
| Acetaminophen (paracetamol), Aspirin, Ibuprofen | anaesthetics, analgetics antalgics, antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs) s |
| Phenytoin, carbamazepine phenobarbital sodiumLamotrigine, Primidone diphenylhydantoin, [Sulfonamides](http://en.wikipedia.org/wiki/Sulfonamides) ([procainamide](http://en.wikipedia.org/wiki/Procainamide)), [Sulfonylureas](http://en.wikipedia.org/wiki/Sulfonylurea) | anticonvulsants (antiepileptics) |
| Iodinated contrast agents ( Ioxaglate, Iohexol, iopamidol, ioversol, Iopromide, Ioxilan, Iodixanol, Gd-GTPA | contrast agents |
| Venofer, Cosmofer, Ferinject, Monofer, Ferrlecit, Ferumoxytol | IV-Iron\*\* |
| Very lowP<0.01 | SonoVue | contrast agents |
| Venofer, Cosmofer, Ferinject, Monofer, Ferrlecit, Ferumoxytol | IV-iron\*\* |

# \*all types of reactions regardless of severity. Rates were obtained from individual box labels, public (internet) information or Summaries of Product Characteristics (SmPCs)

\*\* data uncertain to select the exact category, P = prevalence

Mechanisms of HSRs to IV-iron versus those to other IV drugs

The *mechanisms* *of HSRs* are categorized in many different ways, 4 of which are shown in Fig 1. The oldest and best known is Gell and Coombs’ classical scheme, which distinguishes four types of HSRs, Type I-IV (Gell *et al.*, 1963; Coombs *et al.*, 1968). The system is based on pathophysiological principles and is criticized (Descotes *et al.*, 2001; Rajan, 2003) on the basis that the adverse immune effects of drugs occur mostly via complex mechanisms which cannot be cleanly fitted into Gell and Coomb’s categories. One important example is direct complement (C) activation causing Type I reactions, since these reactions are defined by Gell and Coomb as being solely IgE-mediated.

Among the alternative classifications of HSR mechanisms, Descotes proposed 3 categories: immunoglobulin-mediated, cell-mediated and pseudoallergic (Descotes *et al.*, 2001). Pichler labelled his 5 categories with Greek letters: type  reactions involve cytokine release, -type reactions are immune reactions against biological agents, -type reactions are immune or cytokine imbalance syndromes, -type reactions arise because of cross-reactivity, and -type reactions do not directly involve the immune system (Pichler, 2006). The last included mechanistic scheme was proposed by one of us (Szebeni, 2005), wherein Gell and Coombs’ type I reactions were subdivided according to the mechanism of mast cell (and basophil) activation. The scheme suggests a distinction between direct and receptor-mediated stimulation of mast cells and basophils, with the latter arm subdivided to 1) FcR, 2) anaphylatoxin receptor (ATR, C5aR and C3aR) and 3) both FcR and ATR-mediated mixed responses. The IgE-R-mediated HSRs are the classical type I reactions, while the ATR-mediated release reactions underlie C activation-related pseudoallergy (CARPA) (Szebeni, 2005), which can occur without the presence of any specific antibodies or immune competent cells.

As for mechanistic distinction between IV-iron reactions and other IV-drug-induced reactions, the weight of evidence suggests that IV-iron reactions are not IgE-mediated (Fleming *et al*., 1992;Novey *et al*. 1994). However, other than this conclusion, there is insufficient information to prove any other “immune” mechanism. Among the non-immune mechanisms, there are several lines of indirect evidence suggesting that CARPA may play a causal role in IV-iron reactions. This hypothesis will be described in substantial detail later in this review.

*Risk factors of HSRs to IV-iron versus other IV drugs*

The risk factors for IV-iron reactions include genetic predisposition, general nonspecific factors and unique temporary conditions. Among the genetic predispositions, atopic constitution is the best recognized, in which the patients have an innate proneness for asthma or allergy to drugs, pollens and other allergens (Enright *et al*., 1989, Goss *et al*., 1995, Brannagan, 2002; Laman *et al*., 2005; Hong *et al*., 2012; Kelsall *et al*., 2012, Auerbach *et al*., 1998; 2011; Fletes *et al*., 2001; Fishbane, 2003). The acquired lasting risk factors include, among others, old age, concurrent or past cardiovascular disease, autoimmune diseases and mastocytosis (Ansell *et al*., 1980; Shehadi, 1982; Goss *et al*., 2002; Simons *et al*., 2011), while the acquired temporary risk factors are exemplified by infectious diseases, certain medications (e.g., beta-adrenergic blockers, ACE-inhibitors (Goss *et al*., 2002; Simons *et al*., 2011) and even psychological distress (Lalli, 1974; Misbah *et al*., 1993). We are not aware of significant differences between IV-iron and other IV drugs in relation to the above risk factors.

Unsolved issues in clinical research on HSRs to IV-iron and other IV drugs

As pointed out by Auerbach *et al*, there is an unmet medical need for a uniform and commonly accepted definition of adverse events to iron compounds, the absence of which at present is a major reason for the statement that “reliable comparative safety data do not exist” (Auerbach *et al*., 2010). In fact, one major problem in clinical HSR research is its complex and sometimes confusing terminology.

There is a long list of different descriptive, qualitative and quantitative terms for essentially the same acute illness (abnormal immune stimulation), leading the World Allergy Organization to a Nomenclature Review conference in 2004 (Johansson *et al*., 2004). Subsequently, the list of terms has expanded (Table 3), among which the use of “immunologic” and “non-immunologic” HSRs to differentiate between of IgE-mediated reactions from all others is particularly questionable, since the involvement of IgE or other specific antibodies in HSRs often cannot be proved or has not even been tested (Johansson *et al*., 2004; Kemp *et al*., 2008). This problem applies to all HSRs, including IV-iron reactions.

In addition to the ambiguous terminology, anaphylaxis research is hindered by two other factors: 1) the rarity of severe reactions, making it difficult, if not impossible, to set up comparative trials according to the principles of evidence-based medicine, and 2) the lack of animal models which mimic the symptoms of human HSRs. As for the first problem, instead of Phase I toxicity/safety- evaluation followed by randomized, placebo-controlled clinical trials, clinical evidence in the field of anaphylaxis is mostly based on retrospective analyses of large databases and medical records, which can seldom answer specific, prospective questions regarding safety or efficacy.

The problem of animal models of anaphylaxis lies in the divergence from humans in their sensitivity to different reactogenic drugs, and in the frequency of occurrence and symptoms of reactions. For these reasons there is no validated animal model of human HSRs provoked either by drugs, or other causes, e.g., foods, insect stings, surgery, exercise. Nevertheless, animal models are useful for the study of some common steps in anaphylaxis at the cellular and subcellular level, for example mast cell degranulation (Nauta *et al.*, 2008).

One aspect of progress in this field that awaits professional and regulatory recognition is the use of pig models of CARPA, since pigs, unlike rats and mice, resemble humans in their hemodynamic, hematologic, biochemical and skin responses to many nanomedicines (liposomes, micellar drugs, radiocontrast agents, polymers, antibodies, protein drugs, enzymes) with unique sensitivity and reproducibility (Szebeni *et al.*, 1999b; 2000; 2006; 2007; 2012a, b, c; 2014; Merkel *et al.*, 2011; Dézsi *et al.*, 2014). It is this model that presents both tachyphylactic and non-tachyphylactic reactions and therefore allows prediction of the efficacy of slow infusion and prophylactic desensitization with drug carriers (such as empty liposomes) (Szebeni *et al.*, 1999a; 2012a,b, c; Dézsi *et al.*, 2014). Whether IV-iron nanoparticles will trigger CARPA in pigs awaits experimental exploration.

Table 3. Terms used for different hypersensitivity reactions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Term** | **Type** | **Definition** | **Mechanism** | **Severity** |
| Drug allergy | descriptive | hypersensitivity to drugs  | Any | mild-to-severe |
| Infusion reaction | HSR arising as a consequence of infusion |
| Idiosyncratic reaction | HSR without known reason |
| Anaphylaxis | quantitative  | Severe, life-threatening generalized or systemic HSR  | Any | severe |
| Pseudoallergy  | qualitative | Systemic and/or local signs of HSR | any mechanism with no role of specific IgE, IgG or IgM  | mild-to-severe |
| Non-allergic hypersensitivity |
| Non-immune hypersensitivity |
| Complement-activation-related pseudoallergy (CARPA) | C activation is involved directly or indirectly |
| Immunologic anaphylaxis | qualitative and quantitative | mediated by specific IgE, IgG or IgM | severe |
| Non-immunologic anaphylaxis | Not mediated by specific IgE, IgG or IgM |
| Anaphylactoid reaction | mild-to-severe |
| Type B adverse drug reaction  | Drug dose -independent systemic and/or local signs of HSR\* | Any | severe |

\*Scott *et al.*, 2014.

Current prevention and treatment of HSRs to IV-iron and other IV drugs

The prevention and treatment options for HSRs to IV-iron and other IV drugs differ according to the severity and prevalence of HSRs. For reaction prevention, there are two options: premedication and the use of low reactogenic protocols (LRPs).

The premedication regimes usually include corticosteroids and antihistamines, along with a variety of additional agents, including acetaminophen (paracetamol). However, the efficacy of premedication to prevent mild and moderate HSRs has been queried, and many authors believe that premedication for all patients are not justified: premedication should be reserved only for patients at increased risk (Tramer *et al.*, 2006). Among other causes of skepticism, the benefit of antihistamines has been questioned on the basis that they increase the frequency of ADRs (Lorenz *et al.*, 1985; Baller *et al.*, 1989; Wasserman *et al.*, 2004) and that the symptoms they produce can mimic those of a mild HSR (Auerbach *et al.,* 2010)*.* It has also been shown that acetaminophen is as effective alone as together with antihistamines (Keshavarzian *et al.*, 2007). Taking this evidence together, we conclude that there is now no place for the use of antihistamines for the prevention or treatment of HSRs to iv iron.

The use of LRPs is the other potential safety measure to prevent HSRs to IV drugs. Two groups of IV medicines were shown to benefit most from this approach: therapeutic mAbs and liposomal drugs. LRP for mAbs was introduced by Puchner *et al* (Puchner *et al.*, 2001) to prevent HSRs to infliximab. Their protocol involved an 11-step progressive dose escalation over 4 hours, a technique which was later applied for other antineoplastic mAbs including rituximab, cetuximab and trastuzumab (Duburque *et al.*, 2006; Castells, 2008; Castells *et al.*, 2008; Brennan *et al.*, 2009). The infusion rates and timing of escalation steps were different in the various protocols, and they were often combined with anti-allergic pre-medications. What is common to all LRPs is that the infusion is started at a very low rate carrying 1/1000th to 100th part of the full drug dose in 5-15 min. This priming may serve two functions: 1) desensitization of the patient to the drug and 2) an indication of the presence of hypersensitivity.

The use of LRP to prevent liposome reactions was first applied for the infusion of L-Dox (Gabizon *et al.*, 1998). The liposome infusion was initially administered at a rate of 1 mg Dox/min, and if no reactions occurred, the rate was increased to complete the IV therapy over 1 hour. This method remains the recommended protocol for L-Dox administration today (Doxil prescribing information, 2014).

LRP has also been applied successfully for the prevention of IV-iron reaction in high-risk patients, with a history of life threatening reactions (Altman and Petersen 1988; Monaghan *et al.*, 1994, Hickman *et al.,* 2000). However, because HSRs to IV-iron occur at a low, or very low rate, such approach is not needed in the average, risk factor-free patient.

The treatment options for HSRs to IV drugs and iron are often referred to as “reactive” (Lequerre *et al.*, 2006; Mayer *et al.*, 2006) when they are therapeutic rather than preventive. As summarized in Table 4, these options also depend on the severity of reactions and are identical regardless of the cause of HSR.

Table 4. Reactive treatment options to manage HSRs to intravenous drugs including IV-iron (Rampton *et al*. , 2014)

|  |  |  |
| --- | --- | --- |
|  | **Symptoms** | **Treatment options** |
| **Mild HSRs** | Itching, urticaria, flushing, sensation of heat, slight chest tightness, hypertension, back/joint pains | Stop infusion temporarily and watch symptoms and signs. If symptoms improve the infusion can be restarted cautiously. |
| **Moderate HSRs** | As in mild reaction + cough, chest tightness, nausea, shortness of breath, tachycardia and hypotension | Stop infusion and consider IV-fluids and IV-corticosteroids |
| **Severe HSRs = life threatening anaphylaxis** | As in moderate + Sudden onset and rapid aggravation of symptoms +wheezing, stridor, periorbital edema, cyanosis, loss of consciousness, cardiac /respiratory arrest | As for moderate HSRs + IM or IV adrenalin (epinephrine) + consider B2 agonist inhaler, O2 facemask etc according to local standard anaphylaxis guidelines. |

The treatment of very severe reactions, i.e., anaphylaxis, is special in that these events are very rare, and the medications applied are rarely “evidence-based”. As stated earlier, it is impracticable to perform randomized controlled trials on clinical conditions that are very rare (Black, 1996), a conclusion which also applies to clinical investigations into the most effective treatment of severe anaphylaxis (Ring et al., 2010; Working Group of the Resuscitation Council, UK, 2013). In this context, Ranft et al (2004) concluded that “None of the traditionally applied remedies against anaphylaxis - epinephrine and intravascular volume replacement, histamine receptor blockade, inhaled beta-mimetics and steroids - have been proved efficacious by means of evidence-based medicine – there is a lack of consensus as to the substantial elements of therapy”. Despite the methodological challenges, Ring et al (2010) concluded a best clinical treatment practice for severe anaphylaxis: “Adrenalin (epinephrine) is the essential anti-anaphylactic drug. Glucocorticoids are given in order to prevent a protracted or biphasic course of anaphylaxis; they are of little help in the acute treatment. H1 antagonists are valuable in mild anaphylactic reactions; they should be given intravenously if possible. The replacement of volume is crucial in anti-anaphylactic treatment”. These recommendations are largely in agreement with most major guidelines for the treatment of life threatening anaphylaxis (Simons et al., 2011; Working Group of the Resuscitation Council, UK, 2013).

The anaphylatoxin concept of HSRs to IV-iron and efficacy of LRPs

Perhaps the most important conclusion from the comparison of HSRs to IV-iron and other IV drugs is that, other than prevalence, there are no major qualitative or quantitative differences between these reactions. Considering that the overwhelming majority (77%) of all HSRs are not IgE-mediated (Demoly *et al, 1999*), it seems reasonable to assume that IV-iron reactions could have the same “non-immune” underlying mechanism as the majority of other IV-drugs. One of the “non-immune” mechanisms that have received much attention recently is CARPA, which has been claimed to be a common cause for, or contributing factor to all acute HSRs provoked by any infusion that contains C-activating antibodies or nanoparticles.

Van der Kolk *et al* (van der Kolk *et al.* 2001 ) showed that C activation plays a causal role in the HSRs to rituximab. Evidence accumulated over the past 2 decades (Szebeni J *et al.* 1994-2014) has also indicated the importance of C-activation in the causation of HSRs to liposomes, including L-Dox. For example, a clinical investigation showed that strong C activation in cancer patients infused with L-Dox correlated with the severity and frequency of HSRs, and that the rate of drug infusion was critical to the risk of HSR (Chanan-Khan *et al.*, 2003). The study could even accurately predict the upper threshold of safe initial infusion rate (0.38 mg Doxorubicin/min) on the basis of a significant correlation between initial infusion rate and in vivo production of SC5b-9, an index of C activation. Such measurements and calculations may be useful for the development of LRPs for other reactogenic drugs.

Prior preclinical evidence for C activation underlying the infusion rate-dependence of HSRs was provided in a porcine model of liposome-induced CARPA, wherein the speed of liposome infusion showed remarkable correlation with the rise of pulmonary arterial pressure (Szebeni *et al.*, 2000), which, in turn, was shown to arise as a consequence of C activation-related anaphylatoxin production (Szebeni *et al.*, 1999, 2000). These facts taken together suggest that the slow-infusion-based LRPs may be effective when C activation is a major pathogenic factor for HSRs.

Among further in vivo evidence for CARPA as a common underlying mechanism of HSRs, it has been shown that HSRs not only to liposomes, but also to polymers, dendrimers, carbon nanotubes and a wide range of other nanoparticles are also C activation-related, and the symptoms are similar and closely mimic human HSRs and anaphylaxis (Szebeni, 2012). Studies on the phenomenon have established that the reactogenic C-activating nanoparticles are usually highly charged and/or coated by repetitive surface projections from polymers, carbohydrate, peptides, etc, that bind antigen or pattern recognition molecules (IgM, IgG, C1q, mannose binding lectin (MBL), ficolin). Crystalline surfaces (shown for silica and paclitaxel, Szebeni *et al.,* 2003) as well as 71% cholesterol-containing liposomes, wherein the cholesterol is partially crystallized (Szebeni *et al.,* 200, Baranyi *et al*, 2003) are also effective C activators and inducers of HSR. Since all existing IV iron medicines consist of crystalline iron oxide/hydroxide nanoparticle cores (up to 10-20 nm) and a carbohydrate shell (from mannitol, dextran, gluconate sucrose, carboxymaltose, isomaltoside, etc) (Fütterer *et al,* 2013), preconditions for C activation via crystal- and carbohydrate recognition molecules exist with all IV iron medicines. In addition, some of the iron-carbohydrate complexes can also agglomerate to form large clusters (up to 200 nm) (Fütterer *et al,* 2013), providing further surface for C activation.

Although we are not aware of studies showing C activation by reactogenic IV-iron medicines, a recent study provided evidence for such activation by dextran-coated superparamagnetic iron oxide (SPIO) nanoparticles used as a magnetic resonance imaging (MRI) contrast agent (Banda *et al,* 2014). The latter study also investigated the mechanism of C activation in human and mouse serum and found evidence for prominent involvement of the lectin pathway (via MBL or L-ficolin) and triggering of alternative amplification loop (Banda *et al,* 2014). Because the SPIO nanoparticles in the above study also caused major HSRs in patients, and because the basic structure of all IV-iron medicines and iron-oxide core/dextran shell containing MRI contrast agents are very similar, it is highly likely that C activation by IV-iron can occur in man via the same or similar mechanism and may cause or contribute to the rare occurrence of non-IgE-mediated HSRs.

The above facts and considerations, taken together with the reported success of slow infusion protocols in preventing life-threatening reactions to IV-iron (Altman and Petersen 1988; Monaghan *et al.*, 1994, Hickman *et al.,* 2000) suggest that CARPA, the proposed mechanism of very frequent liposome and antibody and taxane reactions, also represents the most likely mechanism of IV-iron reactions. The difference in prevalence might arise from differences in the extent of C activation and/or the general sensitivity of patients for activation by these agents.

As for the chain of events leading from C activation to HSRs, the anaphylatoxins C3a and C5a bind to mast cells (and basophil leukocytes and macrophages) via specific receptors on these cells, and trigger the release of a great number of vasoactive mediators that cause the symptoms of HSRs (Fig 2).

Fig. 2. Scheme illustrating the anaphylatoxin concept of HSRs caused by drug particles. In the rare patients developing these reactions, iron, or other nanoparticle-based drugs, activate the C system (upper red arrow) that leads to the formation of anaphylatoxins. Their blood level is determined by generation via this activation process, and by consumption, due partly to cellular uptake and partly to metabolism by carboxypeptidases (green). The level in blood determines whether or not anaphylatoxins trigger mast cells for release reaction (lower red arrow). A scheme of C activation (left insert) and the main vasoactive mediators released from mast cells are also shown.

Fig 1 also explains why a low speed of infusion is an effective way of preventing HSRs to all reactogenic drugs, including IV-iron. Namely, anaphylatoxin levels in blood are determined by their production via C activation and their clearance by carboxypeptidases (Campbell *et al.* 2002) and by cellular uptake. Changes in this equilibrium are fast, so that slow infusion may keep the concentration of anaphylatoxins below the HSR threshold of allergy-mediating cells (mast cells, basophils and certain macrophages), while massive and rapid exposure to a C activator may tip the balance towards anaphylatoxin build-up, and hence surpass the HSR threshold (Fig. 1).

Conclusions and Outlook

This paper represents an extension of a previous review of IV-iron reactions, which focused on risk minimization and management (Rampton *et al*, 2014). Here we compare the various features of IV-iron and other IV drug-induced HSRs in order to uncover possible clues regarding their mechanism and how to improve therapy. Our particular scientific question was: “What is the available direct or indirect evidence for shared molecular mechanisms that have implications for the prevention and treatment of HSRs in general, and of IV-iron reactions, in particular?” The comparison focused on the symptoms, prevalence, kinetics, duration, tolerance and molecular mechanisms of HSRs and came to the conclusion that C activation and subsequent anaphylatoxin production may be a common underlying cause for many HSRs to IV drugs, including IV-iron. The review addresses the difficulties of nomenclature and clinical studies in allergy research, and points out that the treatment of IV-iron reactions is based on empiric traditions rather than clinical research. It is also emphasized that, as further evidence becomes available, the recent EMA guidance on risk minimization for very rare IV-iron reactions should be extended or revised with recommendations for specific and effective new interventions against HSRs to iron, for example by using slow infusion-based LRPs that are known to attenuate CARPA. In this context, the anaphylatoxin concept may spur many more C-focused desensitization or treatment ideas.

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Potential Conflict of Interest

JS and SF have nothing to disclose; MH reports minor speaker honoraria from Vifor, Takeda and Pharmacosmos; SH reports personal fees from Pharmacosmos and Vifor, FL reports memberships of advisory boards and/or speaker invitations at symposia supported by Abbvie, Amgen, Pharmacosmos, Keryx, Rockwell, Sanofi, Takeda, Vifor-Fresenius Pharma; SP reports personal fees from Pharmacosmos, outside the submitted work; DSR reports personal fees from Pharmacosmos and Vifor outside the submitted work; GW reports personal fees from Pharmacosmos and Vifor outside the submitted work; JF reports personal fees from Pharmacosmos outside the submitted work.

References

1. Adkinson NFJ, Essayan D, Gruchalla R, Haggerty H, Kawabata T, Sandler JD, *et al* (2002). Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. J Allergy Clin Immunol. 109: S461-478.
2. Altman LC, Petersen PE (1988). Successful prevention of an anaphylactoid reaction to iron dextran. Ann Intern Med; 109:346-347.
3. Alving CR, Kinsky SC, Haxby JA, Kinsky CB (1969). Antibody binding and complement fixation by a liposomal model membrane. Biochemistry 8: 1582-1587.
4. Ansell G, Tweedie MC, West CR, Evans P, Couch L (1980). The current status of reactions to intravenous contrast media. Invest Radiol. 15(6 Suppl): S32-S39.
5. Auerbach M, Ballard H (2010). Clinical use of intravenous iron: administration, efficacy, and safety. Hematology. Am Soc Hematol Educ Program 2010: 338-347.
6. Auerbach M, Chaudhry M, Goldman H, Ballard H (1998). Value of methylprednisolone in prevention of the arthralgia-myalgia syndrome associated with the total dose infusion of iron dextran: a double blind randomized trial. J Lab Clin Med 131: 257-260.
7. Auerbach M, Pappadakis JA, Bahrain H, Auerbach SA, Ballard H, Dahl NV (2011). Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. Am J Hematol 86: 860-862.
8. Bailie GR (2012). Comparison of rates of reported adverse events associated with i.v. iron products in the United States. Am J Health Syst Pharm 69: 310-320.
9. Bailie GR, Clark JA, Lane CE, Lane PL (2005). Hypersensitivity reactions and deaths associated with intravenous iron preparations. Nephrol Dial Transplant. 20: 1443-1449.
10. Bailie GR, Horl WH, Verhoef JJ (2011). Differences in spontaneously reported hypersensitivity and serious adverse events for intravenous iron preparations: comparison of Europe and North America. Arzneimittelforschung. 61: 267-275.
11. Bailie GR, Verhoef JJ (2012). Differences in the reporting rates of serious allergic adverse events from intravenous iron by country and population. Clin Adv Hematol Oncol 10: 101-108.
12. Baller D, Huchzermeyer H (1989). Histamine effects on the heart with special reference to cardiac side effects of H2 receptor antagonists. Klin Wochenschr 67: 743-755.
13. Banda NK, Mehta G, Chao Y, Wang G, Inturi S, Fossati-Jimack L, Botto M, Wu L, Moghimi S, Simberg D (2014). Mechanisms of complement activation by dextran-coated superparamagnetic iron oxide (SPIO) nanoworms in mouse versus human serum. Part Fibre Toxicol.11:64-74
14. Baranyi L, Szebeni J, Savay S, Bodo M, Basta M, Bentley TB, Bunger R, Alving CR (2003). Complement-dependent shock and tissue damage induced by intravenous injection of cholesterol-enriched liposomes in rats. J Applied Res 3: 221-231.
15. Bircher AJ, Auerbach M (2014). Hypersensitivity from intravenous iron products. Immunol Allergy Clin North Am. 34: 707-723.
16. Black N (1996). Why we need observational studies to evaluate the effectiveness of health care. BMJ. 312: 1215-1218.
17. Brannagan TH (2002). Intravenous gammaglobulin (IVIg) for treatment of CIDP and related immune-mediated neuropathies. Neurology. 59 (Suppl 6): S33-S40.
18. Brennan PJ, Rodriguez BT, Hsu FI, Sloane DE, Castells MC (2009). Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol. 124: 1259-1266.
19. Brown SG (2004). Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 114: 371-376.
20. Campbell WD, Lazoura E *et al* 2002. Inactivation of C3a and C5a octapeptides by carboxypeptidase R and carboxypeptidase N. Microbiol Immunol 46: 131-134.
21. Castells MC (2008). Hypersensitivity to antineoplastic agents. Curr. Pharm. Des. 14: 2892-2901.
22. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, *et al* (2008). Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol. 122: 574-580.
23. Chanan-Khan A, Szebeni J, Savay S, Liebes L, Rafique NM, Alving CR, *et al* (2003). Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil): possible role in hypersensitivity reactions. Ann Oncol 14: 1430-1437.
24. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J (2004). On the relative safety of parenteral iron formulations. Nephrol Dial Transplant 19: 1571-1575.
25. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J (2006). Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 21: 378-382.
26. Coombs RRA, Gell PGH (1968). Classification of allergic reactions responsible for drug hypersensitivity reactions. In: Coombs RRA, Gell PGH (eds). Clinical Aspects of Immunology, 2nd Ed., edn. Philadelphia, PA: Davis. pp 575-596.
27. Critchly JU, Dunbar YE (2007). Adverse events associated with intravenous iron infusion (low-molecular-weight iron dextran and iron sucrose): a systematic review. TATM 9: 8-36.
28. Demoly P, Lebel B, Messaad D, Sahla H, Rongier M, Daures JP, Godard P, Bousquet J (1999). Predictive capacity of histamine release for the diagnosis of drug allergy. Allergy 54: 500–506.
29. Descotes J, Choquet-Kastylevsky G (2001). Gell and Coombs's classification: is it still valid? Toxicology 158: 43-49.
30. Dézsi L, Fülöp T, Mészáros T, Szénási G, Urbanics R, Vázsonyi C, *et al*. (2014). Features of complement activation-related pseudoallergy to liposomes with different surface charge and PEGylation: Comparison of the porcine and rat responses. J Contr Release. 195: 2-10.
31. Doxil prescribing information, Doxil.com (2014) https://www.doxil.com/shared/product/doxil/prescribing-information.pdf
32. Duburque C, Lelong J, Iacob R, Seddik M, Desreumaux P, Fournier C, *et al* (2006). Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. Aliment Pharmacol Ther 24: 851-858.
33. EMA-CHMP (2013). New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines Vol. EMA/579491/2013, pp 1-3: http://www.ema.europa.eu/docs/en\_GB/document\_library/Referrals\_document/IV\_iron\_31/WC500151308.pdf.
34. Enright T, Chua-Lim A, Duda E, Lim DT (1989). The role of a documented allergic profile as a risk factor for radiographic contrast media reaction. Ann Allergy 62: 302-305.
35. Fishbane S (2003). Safety in iron management. Am J Kidney Dis. 41(5 Suppl): 18-26.
36. Fleming LW, Stewart WK, Parratt D (1992). Dextran antibodies, complement conversion and circulating immune complexes after intravenous iron dextran therapy in dialysed patients. Nephrol.Dial.Transplant. 7(1): 35-39.
37. Fletes R, Lazarus JM, Gage J, Chertow GM (2001). Suspected iron dextran-related adverse drug events in hemodialysis patients. Am.J.Kidney Dis. 37(4): 743-749.
38. [Fütterer S](http://www.ncbi.nlm.nih.gov/pubmed/?term=F%C3%BCtterer%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23998966), [Andrusenko I](http://www.ncbi.nlm.nih.gov/pubmed/?term=Andrusenko%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23998966), [Kolb U](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kolb%20U%5BAuthor%5D&cauthor=true&cauthor_uid=23998966), [Hofmeister W](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hofmeister%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23998966), [Langguth P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Langguth%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23998966). (2013) Structural characterization of iron oxide/hydroxide nanoparticles in nine different parenteral drugs for the treatment of iron deficiency anaemia by electron diffraction (ED) and X-ray powder diffraction (XRPD). [J Pharm Biomed Anal.](http://www.ncbi.nlm.nih.gov/pubmed/23998966) 86:151-60
39. Gabizon AA, Muggia FM (1998). Initial clinical evaluation of pegylated liposomal doxorubicin in solid tumors. In: Woodle MC, G. S (eds). Long-Circulating Liposomes: Old Drugs, New Therapeutics, edn. Austin, TX: Landes Bioscience. pp 155-174.
40. Gell PGH, Coombs RRA (1963). Classification of allergic reactions underlying disease. edn. Blackwell: Oxford.
41. Goss JE, Chambers CE, Heupler FA, Jr. (1995). Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures: guidelines for prevention, diagnosis, and treatment. Laboratory Performance Standards Committee of the Society for Cardiac Angiography and Interventions. Cathet.Cardiovasc.Diagn. 34(2): 99-104.
42. Hickman MA, Bernstein IL, Palascak JE. Successful administration of iron dextran in a patient who experienced a life threatening reaction to intravenous iron dextran. Ann Allergy Asthma Immunol 2000; 84(2):262-263
43. Hong DI, Bankova L, Cahill KN, Kyin T, Castells MC (2012). Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. Expert.Rev.Clin.Immunol. 8(1): 43-52.
44. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, *et al*. (2004). Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J.Allergy Clin.Immunol. 113(5): 832-836.
45. Kdigo, Improving Global O, Anemia Work G (2012). KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney inter., Suppl. 2012; 2: 279-335.
46. Kelsall J, Rogers P, Galindo G, De Vera MA (2012). Safety of infliximab treatment in patients with rheumatoid arthritis in a real-world clinical setting: description and evaluation of infusion reactions. J Rheumatol. 39(8): 1539-1545.
47. Kemp SF, Lockey RF, Simons FE (2008). Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 63(8): 1061-1070.
48. Keshavarzian A, Mayer L, Salzberg B, Garone M, Finkelstein W, Cappa J, *et al*. (2007). A multicenter retrospective experience of infliximab in Crohn's disease patients: infusion reaction rates and treatment persistency. Gastroenterol.Hepatol.(N.Y.). 3(5): 381-390.
49. Lalli AF (1974). Urographic contrast media reactions and anxiety. Radiology. 112(2): 267-271.
50. Laman CA, Silverstein SB, Rodgers GM (2005). Parenteral iron therapy: a single institution's experience over a 5-year period. J Natl.Compr.Canc.Netw. 3(6): 791-795.
51. Lang DM, Alpern MB, Visintainer PF, Smith ST (1991). Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann.Intern.Med. 115(4): 270-276.
52. Lazarou J, Pomeranz BH, Corey PN (1998). Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. JAMA 279: 1200-1205.
53. Lequerre T, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, *et al*. (2006). Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 33(7): 1307-1314.
54. Lorenz W, Doenicke A (1985). H1 and H2 blockade: a prophylactic principle in anesthesia and surgery against histamine-release responses of any degree of severity: Part 1. N.Engl.Reg Allergy Proc. 6(1): 37-57.
55. Mayer L, Young Y (2006). Infusion reactions and their management. Gastroenterol.Clin.North Am. 35(4): 857-866.
56. Merkel OM, Urbanics R, Bedőcs P, Rozsnyay Z, Rosivall L, Toth M, *et al*. (2011). In vitro and in vivo complement activation and related anaphylactic effects associated with polyethylenimine and polyethylenimine-grafted-poly (ethylene glycol) block copolymers. Biomaterials 32: 4936-4942.
57. Misbah SA, Chapel HM (1993). Adverse effects of intravenous immunoglobulin. Drug Saf. 9: 254-262.
58. Monaghan MS, Glasco G, St John G, Bradsher RW, Olsen KM. (1994). Safe administration of iron dextran to a patient who reacted to the test dose. South Med J. 87:1010-2.
59. Nauta AJ, Engels F, Knippels LM, Garssen J, Nijkamp FP, Redegeld FA (2008). Mechanisms of allergy and asthma. European Journal of Pharmacology 585: 354–360.
60. Novey HS, Pahl M, Haydik I, Vaziri ND (1994). Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. Ann.Allergy 72(3): 224-228.
61. Pichler WJ (2006). Adverse side-effects to biological agents. Allergy 61: 912-920.
62. Puchner TC, Kugathasan S, Kelly KJ, Binion DG (2001). Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. Inflamm Bowel Dis 7(1): 34-37.
63. Rajan TV (2003). The Gell–Coombs classification of hypersensitivity reactions: a re-interpretation. Trends in Immunol 24: 376-379.
64. Rampton G, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, *et al*. (2014). Hypersensitivity reactions to intravenous iron: guidance for risk minimisation and management. Haematologica 99: 1671-1676.
65. Ranft A, Kochs EF (2004). [Treatment of anaphylactic reactions: a review of guidelines and recommendations]. Anasthesiol.Intensivmed.Notfallmed.Schmerzther. 39(1): 2-9.
66. Ring J, Grosber M, Mohrenschlager M, Brockow K (2010). Anaphylaxis: acute treatment and management. Chem.Immunol.Allergy. 95:201-10. doi: 10.1159/000315953. Epub;%2010 Jun 1.: 201-210.
67. Ring J, Messmer K (1977). Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1(8009): 466-469.
68. Scott S, Thompson J (2014). Adverse drug reactions. Anest Intens Care Med 15: 245-249.
69. Shehadi WH (1982). Contrast media adverse reactions: occurrence, recurrence, and distribution patterns. Radiology 143(1): 11-17.
70. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, *et al*. (2011). World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 4(2): 13-37.
71. Szebeni J, Alving CR, Savay S, Barenholz Y, Priev A, Danino D, Talmon Y. (2001) Formation of complement-activating particles in aqueous solutions of Taxol: possible role in hypersensitivity reactions. International Immunopharmacology 1: 721–735
72. Szebeni J (2005). Complement activation-related pseudoallergy: a new class of drug-induced immune toxicity. Toxicology 216: 106-121.Szebeni J (2012). Hemocompatibility testing for nanomedicines and biologicals: predictive assays for complement mediated infusion reactions. Eur. J. Nanomed. 5: 33-53.
73. Szebeni J (2014). Complement activation-related pseudoallergy: A stress reaction in blood triggered by nanomedicines and biologicals. Mol. Immunol. 61: 163-173.
74. Szebeni J, Alving CR, Rosivall L, Bünger R, Baranyi L, Bedöcs P, *et al*. (2007). Animal models of complement-mediated hypersensitivity reactions to liposomes and other lipid-based nanoparticles. Journal of liposome research 17(2): 107-117.
75. Szebeni J, Baranyi L, Sávay S, Bodó M, Milosevits J, Alving CR, *et al*. (2006). Complement activation-related cardiac anaphylaxis in pigs: role of C5a anaphylatoxin and adenosine in liposome-induced abnormalities in ECG and heart function. Am. J. Physiol. 290: H1050-1058.
76. Szebeni J, Baranyi L, Savay S, Bodo M, Morse DS, Basta M, *et al*. (2000). Liposome-induced pulmonary hypertension: properties and mechanism of a complement-mediated pseudoallergic reaction. Am.J.Physiol Heart Circ.Physiol. 279(3): H1319-H1328.
77. Szebeni J, Bedőcs P, Csukás D, Rosivall L, Bunger R, Urbanics R (2012a). A porcine model of complement-mediated infusion reactions to drug carrier nanosystems and other medicines. Adv Drug Deliv Rev. 64: 1706-1716.
78. Szebeni J, Bedőcs P, Rozsnyay Z, Weiszhár Z, Urbanics R, Rosivall L, *et al*. (2012b). Liposome-induced complement activation and related cardiopulmonary distress in pigs: factors promoting reactogenicity of Doxil and AmBisome. Nanomedicine NBM 8: 176-184.
79. Szebeni J, Bedőcs P, Urbanics R, Bunger R, Rosivall L, Tóth M, *et al*. (2012c). Prevention of infusion reactions to PEGylated liposomal doxorubicin via tachyphylaxis induction by placebo vesicles: a porcine model. J. Contr. Rel. 160: 382-387.
80. Szebeni J, Fontana JL, Wassef NM, Mongan PD, Morse DS, Dobbins DE, *et al*. (1999a). Hemodynamic changes induced by liposomes and liposome-encapsulated hemoglobin in pigs: a model for pseudoallergic cardiopulmonary reactions to liposomes. Role of complement and inhibition by soluble CR1 and anti-C5a antibody. Circulation. 99(17): 2302-2309.
81. Szebeni J, Muggia F, Gabizon A, Barenholz Y (2011a). Activation of complement by therapeutic liposomes and other lipid excipient-based therapeutic products: prediction and prevention. Advanced drug delivery reviews 63(12): 1020-1030.
82. Szebeni J, Wassef NM, Spielberg H, Rudolph AS, Alving CR (1994). Complement activation in rats by liposomes and liposome-encapsulated hemoglobin: evidence for anti-lipid antibodies and alternative pathway activation. Biochem Biophys Res Comm 205: 255-263.
83. Tramer MR, von EE, Loubeyre P, Hauser C (2006). Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. BMJ. 333(7570): 675.
84. van der Kolk LE, Grillo-López AJ, Baars JW, Hack CE, van Oers MH (2001 ). Complement activation plays a key role in the side-effects of rituximab treatment. Br J Haematol 115: 807-811.
85. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC (2004). Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 31(10): 1912-1917.
86. Working Group of the Resuscitation Committee? (2013). Emergency treatment of anaphylactic reactions - Guideline for health care providers. Resuscitation Council (UK) http://www.resus.org.uk/pages/reaction.pdf
87. Wysowski DK, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C (2010). Use of parenteral iron products and serious anaphylactic-type reactions. American Journal of Hematology 85(9): 650-654.

Fig. 1. Hypersensitivity reaction parameters and their different classifications

Fig. 2. Scheme illustrating the anaphylatoxin concept of HSRs. Iron, as well as other nanoparticles activate the C system (upper red arrow) that leads to the formation of anaphylatoxins. Their blood level is determined by generation via this activation process, and by consumption, due partly to cellular uptake and partly to metabolism by carboxypeptidases (green). The level in blood determines whether or not anaphylatoxins trigger mast cells for release reaction (lower red arrow). A scheme of C activation (left insert) and the main vasoactive mediators released from mast cells are also shown.