

New concepts in the management of adverse drug reactions

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ABSTRACT

Our understanding of drug reactions and their management has changed markedly in recent years with the development of several new concepts. Epidermal cell death seen in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) may result from Fas-Fas ligand-mediated apoptosis. Intravenous immunoglobulin (IVIG) contains anti-Fas antibodies that can abrogate apoptosis. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to healing. Furthermore, several studies have dispelled the myth of sulfonamide cross-reactivity. Immune-mediated reactions against antibacterial sulfonamides are directed against two unique side chains that non-antibacterial sulfonamides do not contain. Certain patients seem to have a genetic predisposition for "multiple drug sensitivities." Hence, they may react to several drugs that are not necessarily cross-reacting. Also, multiple studies have shown that IgE-mediated nonsteroidal anti-inflammatory drugs (NSAIDs) cross-reactivity is uncommon. Rather, it is cyclooxygenase (COX) 1 inhibition that results in pseudoallergic reactions to multiple NSAIDs. Several studies have indicated that selective COX-2 inhibitors can be safely administered in patients with aspirin-exacerbated respiratory disease and NSAID-induced cutaneous reactions, although their use has been curtailed by their cardiovascular side effects. Biological agents, such as infliximab, are being increasingly used for a variety of diseases and have caused adverse reactions in some patients. Studies differ as to whether concomitant immunosuppressive use with infliximab affects the development of drug-specific antibodies and infusion reactions. Successful desensitization protocols have been developed for reactions to some of these agents.

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Management of most adverse drug reactions has been limited to immediate discontinuation of the offending drug, prompt symptomatic treatment, and avoidance of cross-reacting drugs. In the absence of an effective alternative medication, desensitization has been successful to a limited number of drugs. In recent years, new concepts have been developed regarding the following: (1) therapeutic agents for treatment of certain severe reactions, (2) cross-reactivity among similar medications, and (3) desensitization to biological agents. This article will focus on a few selected issues, *viz.*, the use of immunoglobulin therapy in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the cross-reactivity among sulfonamides and among nonsteroidal anti-inflammatory drugs (NSAIDs), and the desensitization to certain biological agents.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) FOR SJS AND TEN

Currently, SJS and TEN, which were previously described as separate entities, are considered a continuum of a bullous syndrome. The manifestations may range from erythema multiforme to severe lesions of the skin and mucous membranes. Various degrees of keratinocyte cell death result in subepidermal separation. Often, the syndrome is classified according to the percentage of body surface area (BSA) of epidermal detachment: SJS, <10% BSA; TEN, >30% BSA; and SJS-TEN overlap, 10–30% BSA.¹ The syndrome usually is caused by medications, most commonly antibacterial sulfonamides, anticonvulsants, NSAIDs, and allopurinol.² The combined annual incidence of SJS and TEN is ~2 cases per million population.³ Even though SJS and TEN are rare, they are associated with high mortality—1–5% in SJS^{4,5} and 20–35% in TEN.^{3,5} Over the years, systemic corticosteroids have been reported to be associated with better outcome by some^{6,7} but not by others.^{8,9} Hence, their use in this syndrome remains controversial.

In the last 10 years, our understanding of the mechanism of SJS and TEN has significantly improved.¹⁰ Epidermal cell death and sloughing seen in TEN have been shown to result from apoptosis.¹¹ Keratinocyte apoptosis may be principally mediated through the increased expression of Fas ligand (FasL) on the kera-

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tinocyte surface and its binding to the Fas (CD95) receptor.^{11,12} Abe *et al.*¹³ analyzed sera from patients with SJS, TEN, erythema-multiforme-type drug eruption, and healthy controls. They found significantly elevated soluble FasL concentrations only in those patients with SJS and TEN. Furthermore, serum levels of soluble FasL declined with clinical improvement.

Fas-blocking antibodies have been shown in significant quantities in intravenous immunoglobulin (IVIG) preparations^{12,14} and thus IVIG is expected to abrogate Fas-mediated apoptosis in TEN. In addition, IVIG might have a therapeutic effect through its high content of a wide variety of autoantibodies, antiidiotype antibodies, and complement components. However, *in vitro* studies have shown conflicting results regarding the effect of IVIG, possibly because of differences in experimental conditions.¹⁵ Several clinical studies on the efficacy of IVIG treatment in SJS and TEN have been published in recent years and recently have been reviewed.¹⁰

Viard *et al.*¹² treated 10 patients with SJS or TEN, affecting 5–60% (mean, 28.5%) of BSA, using IVIG in doses ranging from 0.2 to 0.75 g/kg daily for 4 consecutive days. All patients showed arrest of skin disease progression within 24–48 hours and rapid skin healing within 4–12 days (mean, 6.9 days). Since the publication of that study, the use of IVIG in TEN has increased, in part because of the absence of effective alternative therapies.

In a retrospective study¹⁶ of 16 patients with biopsy-proven TEN (BSA, 12–90%) who were treated with IVIG, the observed mortality was compared with expected mortality using a validated predictor score for TEN (SCORTEN).¹⁷ All patients, except one, received 1 g/kg daily of IVIG for 4 consecutive days. The actual mortality was limited to one patient (6.25%) whereas the expected mortality was 5.81 patients (36.3%); *i.e.*, an 83% reduction.

In another larger series¹⁸ from multiple centers, retrospective analysis of 48 patients with TEN (BSA, 10–95%; mean, 44.8%) were treated for 1–5 days (mean, 4 days) with a mean total IVIG of 2.7 g/kg (range, 0.65–5.8 g/kg). Cessation of progression of skin lesions was noted after 1–6 days, with 12% mortality. Several factors were considered by the authors as being associated with a lack of response to IVIG including older age, greater area of epidermal detachment, concomitant disease, delay in time to IVIG administration, and lower mean dose of IVIG.

Trials of IVIG that were limited to children with SJS and TEN showed both efficacy and safety.¹⁰ Morici *et al.*¹⁹ noted enhanced improvement in 6 children with SJS treated within a few days of onset with a single IVIG infusion of 1.5–2 g/kg. Tristani-Firouzi *et al.*²⁰ reported an impressive therapeutic effect of IVIG in 8 children with severe TEN using a dose of 0.5–0.75

g/kg daily for 4 consecutive days. The average time to the arrest of progression was 2.1 days and to complete reepithelization was 8.1 days, without any deaths.

On the other hand, several researchers have reported poor outcomes with IVIG use in SJS and TEN. Bachot *et al.*²¹ conducted a prospective, open trial of 34 consecutive patients with biopsy-confirmed SJS, TEN, or overlap who were admitted 1–9 days (mean, 4.1 days) after onset of symptoms. Within 2 days of admission, 31 patients were treated with a single dose of 2 g/kg of IVIG. Death occurred in 11 (32%) versus the SCORTEN-predicted 8.2 deaths (24%), with the excess mortality mainly in elderly patients. At day 3, epidermal detachment progressed in 22 patients, remained unchanged in 7 patients, and regressed in 4 patients. Unexpectedly, progression of epidermal detachment was associated with earlier treatment with IVIG (within 4 days of onset), suggesting that IVIG did not affect the natural course of the skin lesions.

In a retrospective cohort review,²² 16 patients with TEN and SJS-TEN overlap who received a mean dose of IVIG of 0.7 g/kg (range, 0.5–1.4 g/kg) daily for a mean of 4 days (range, 2–8 days) were compared with 16 historical controls. Both groups were found to be well matched except for a significantly longer delay to admission in the control group (9.1 days versus 4.8 days). Although the investigators reported no statistically significant differences in mortality or progression of skin lesions, there were two fewer deaths in the treated group (4 versus 6). It is worth noting, however, that the lower mortality in the IVIG group may be partly because of earlier treatment.

Brown *et al.*²³ also conducted a retrospective review in which they compared 24 patients with TEN treated with IVIG (400 mg/kg per day for 4 days) with a historical control group of 21 patients. Despite similar average SCORTEN between the two groups, the overall mortality was higher in the IVIG group than in the controls (41.7% versus 28.6%), but this difference was not statistically significant. The number of complications per patient was significantly higher in the IVIG group (2.8 versus 1.7 per patient). However, there was a trend toward a greater delay to admission in the IVIG group that may have confounded the observed effects and partly explain both the greater number of complications and the higher mortality in the IVIG group.

The discrepancies in the aforementioned findings may be caused by differences in the patients' ages, severity of lesions, time of starting treatment, IVIG preparations, and doses used. Batch-to-batch variability in the anti-Fas antibody content has been reported and can be of great significance.¹⁸ For example, Bachot *et al.* used a single brand of IVIG in 30 of 34 patients. Their negative results may be in part because of a possible low content of anti-Fas antibody in that particular preparation. Finally, some studies based their

Table 1 Common sulfonamide preparations

Antibacterial	Non-antibacterial
Sulfacetamide	Acetazolamide
Sulfadiazine	Bumetanide
Sulfamerazine	Chlorpropamide
Sulfamethazine	Chlorthalidone
Sulfamethizole	Dapsone
Sulfamethoxazole	Diazoxide
Sulfamoxole	Furosemide
Sulfapyridine	Glipizide
Sulfisoxazole	Glyburide
	Hydrochlorothiazide
	Metolazone
	Probenecid
	Sulfasalazine
	Sumatriptan
	Tolbutamide
	Torsemide
	Valdecixib

conclusions on comparisons with historical control groups that likely had received different supportive and medical care.^{20–23} Hence, the observed beneficial effects of IVIG may be overestimated in these studies.

To sort out the influence of such variables and reach a clearer decision on the role of IVIG therapy in SJS and TEN, well-designed studies are needed. Ideally, large numbers of patients need to be enrolled in multicenter, double-blind, placebo-controlled, randomized clinical trials, using a selected small number of IVIG preparations and dosages, and preset criteria for inclusion and evaluation.

NEW CONCEPTS IN CROSS-REACTIVITY AMONG SIMILAR DRUGS

Patients with a history of drug reactions are generally at an increased risk for adverse reactions to other drugs, particularly those that have similar structures. The underlying mechanism of developing “multiple drug allergies” to non-cross-reactive drugs is not clear and probably involves, at least partly, genetic factors (gene polymorphisms). Recently, data have been accumulating to indicate that immunologic cross-reactivity is not universal among drugs of similar structures, such as sulfonamide preparations and NSAIDs.

Sulfonamide Preparations

Sulfonamides comprise a large number of therapeutic agents that contain a sulfa moiety and generally are divided into two groups: antibacterial sulfonamides and non-antibacterial sulfonamides (Table 1). Antibacterial sulfonamides contain two specific side chains

that account for the hypersensitivity reactions to these medications: an N1 nitrogen-containing heterocyclic ring and an N4 arylamine group. IgE responses to antibacterial sulfonamides are directed at the N1 substituent whereas nearly all other non-type I hypersensitivity reactions including sulfonamide hypersensitivity syndrome, SJS, and TEN are mediated by the hydroxylamine metabolites of the N4 arylamine group.²⁴

Nevertheless, even in the presence of an N1 heterocyclic ring, the potential for immunologic cross-reactivity can be determined by the presence and location of methyl groups.²⁵ Preparations that have a single methyl group on the second carbon from the sulfonamide group at the N1 position generally are cross-reactive, *e.g.*, sulfamethoxazole and sulfamerazine. On the other hand, preparations with no methyl group (*e.g.*, sulfapyridine) or with more than one methyl group (*e.g.*, sulfamoxole) are less likely to cross-react with those that have a single methyl group.²⁵ Hence, even among arylamine-containing antibacterial sulfonamides, cross-reactivity is not universal.

For many years, there has been concern that the sulfa moiety in antibacterial sulfonamides could cross-react with non-antibacterial sulfonamide derivatives (Table 1). In contrast to the antibacterial group, non-antibacterial sulfonamides do not possess an N1 heterocyclic ring or an arylamine group—the two structural elements that are critical for the development of immune response and cross-reactivity among sulfonamides. Therefore, cross-reactivity between the two groups of sulfonamides is highly unlikely because of the stereospecificity of the immune reaction.²⁶ A lack of cross-reactivity has been shown by *in vitro* studies.²⁶

A meta-analysis of data on celecoxib, a non-arylamine-containing sulfonamide anti-inflammatory agent, revealed no increased risk of allergic reactions in subjects with a history of antibacterial sulfonamide reaction.²⁷ The literature used to support the concept of cross-reactivity between sulfonylarylamines and non-sulfonylarylamines has been reviewed critically by Johnson *et al.*,²⁸ who concluded that there is no convincing evidence for such cross-reactivity.

Despite the paucity of evidence of cross-reactivity, there is a common belief that all sulfonamides are contraindicated in patients with any sulfa reaction. Using the General Practice Research Database in the United Kingdom, Strom *et al.*²⁹ conducted a retrospective cohort study on 20,226 patients who had received prescriptions for non-antibacterial sulfonamides at least 60 days after receiving a systemic antibacterial sulfonamide. Patients with hypersensitivity to the latter were compared with those without. They noted that 9.9% of patients with prior hypersensitivity to antibacterial sulfonamides reacted to subsequent intake of a non-antibacterial sulfonamide (odds ratio, 2.8). How-

ever, patients who had a history of antibacterial sulfonamide reaction also showed an even greater risk of reaction to penicillin (odds ratio, 3.9), a structurally unrelated agent. Thus, the increased risk of allergic reactions to various sulfonamide preparations among certain subjects is more likely to be caused by a genetic predisposition to multiple drug sensitivities rather than a true cross-reactivity.

Nonsteroidal Anti-Inflammatory Drugs

With very few exceptions, the chemical structures of NSAIDs, including aspirin, are so diverse that an IgE antibody to a particular one does not recognize other NSAIDs.³⁰ Reactions to a single NSAID can be IgE mediated. However, pseudoallergic cross-reactivity between several NSAIDs is more likely to be mediated through cyclooxygenase (COX) inhibition. Aspirin and NSAIDs exert their effect primarily through inhibiting the COX pathway, which has at least two isoforms.³⁰ COX-1 is the constitutive form, is expressed in most tissues and platelets, and is the main source of prostaglandin E₂. COX-2 is the inducible form and is expressed in response to proinflammatory agents in epithelial cells, fibroblasts, eosinophils, monocytes, and macrophages.³¹ Although the anti-inflammatory actions of NSAIDs seem to be mediated through inhibiting COX-2, pseudoallergic reactions seem to be related to COX-1 inhibition. Specifically, inhibition of COX-1 results in decreased synthesis of prostaglandin E₂, leading to decreased inhibition of 5-lipoxygenase and subsequent overproduction and release of powerful proinflammatory and bronchoconstrictor agents, *viz.*, cysteinyl leukotrienes (Cys-LTs).^{32,33} Hence, agents that inhibit COX-2 but not COX-1 may offer a safe alternative in patients with aspirin-exacerbated respiratory disease (AERD) and NSAID-induced cutaneous reactions.

Aspirin and other NSAIDs can be divided into separate groups based on their COX inhibition (Table 2). Non-salicylate analgesics such as acetaminophen as well as certain salicylate derivatives such as sodium salicylate do not inhibit COX enzymes at usual doses, but there is some risk of COX-1 inhibition with high doses.³⁰ Nimesulide and meloxicam preferentially inhibit COX-2 although they can inhibit COX-1 at high doses. The selective COX-2 inhibitors, rofecoxib and valdecoxib, do not inhibit the COX-1 isoform and are expected to be tolerated by patients with AERD and NSAID-induced cutaneous reactions. Etoricoxib, a newer selective COX-2 inhibitor, currently is being used in some countries and awaiting Food and Drug Administration approval in the United States.

In a placebo-controlled, single-blind oral challenge study, Bavbek *et al.*³⁴ assessed the tolerability of usual doses of three COX-2 inhibitors in 127 subjects with a

Table 2 Classification of common NSAIDs according to cyclooxygenase inhibition

Drug Class	Generic Names
Preferential COX-1 inhibitors	Diclofenac Etodolac Ibuprofen Indomethacin Ketoprofen Ketorolac Nabumetone Naproxen Piroxicam
Inhibitors of COX-1 only at high doses	Acetaminophen Salsalate
Preferential COX-2 inhibitors; COX-1 inhibitor at high doses	Meloxicam Nimesulide
Selective COX-2 inhibitors	Etoricoxib Rofecoxib Valdecoxib

history of various reactions to aspirin or NSAIDs. Positive oral challenges were observed in 14.3% (18/127) to nimesulide, 8.1% (5/61) to meloxicam, and 2.0% (1/51) to rofecoxib. Interpretation of this study and of a similar one³⁵ is limited by the lack of confirmatory challenges with the implicated drug.

AERD is observed in 5–20% of adult asthmatic patients.³⁶ Celik *et al.*³³ showed that increased Cys-LT levels after aspirin stimulation of peripheral blood leukocytes was unique to aspirin-intolerant asthmatic patients and not present in aspirin-tolerant asthmatic patients or healthy controls. This suggests that the increased Cys-LT production in aspirin-intolerant asthmatic patients may result in part from an abnormal 5-lipoxygenase pathway.

Despite the lack of COX-1 inhibition by the newer selective COX-2 inhibitors, many physicians have avoided prescribing these medications to patients with AERD because of package insert warnings. However, in recent years a number of well-designed studies have indicated that celecoxib,^{37,38} rofecoxib,^{39,40} and etoricoxib⁴¹ were safe in AERD. Stevenson *et al.*³⁹ assessed the cross-reactivity between rofecoxib and aspirin in AERD who had never previously taken rofecoxib. Patients who completed an oral single-blinded placebo challenge without any significant variation in FEV₁ underwent a double-blind rofecoxib challenge, followed 2 days later by an oral single-blind aspirin confirmatory challenge. Patients were allowed to continue using leukotriene antagonists and corticosteroids (nasal, bronchial, or systemic) during the study. All patients experienced nasal and/or respiratory reactions

to aspirin. There were no statistically significant differences in nasoocular scores or in FEV₁ with rofecoxib (at both 12.5- and 25-mg doses) when compared with placebo. The authors pointed out that the study participants had never previously ingested rofecoxib, *i.e.*, excluding the possibility of an IgE-mediated reaction to rofecoxib. This is important because an IgE-mediated reaction to rofecoxib is a potential confounder in some studies that reported COX-1 cross-reactivity.

The lack of cross-reactivity between selective COX-2 and COX-1 inhibitors has been established in AERD. The role of selective COX-2 inhibitor cross-reactivity in patients with cutaneous reactions to COX-1 inhibitors also is becoming clearer. Cutaneous reactions to COX-1 inhibitors can occur in patients with underlying cutaneous disease, particularly urticaria, as well as in those who are apparently healthy. Cross-reactivity among NSAIDs in patients with chronic idiopathic urticaria (CIU) is caused by COX-1 inhibition and increased synthesis of CysLTs. Therefore, as in AERD, COX-2 inhibitors are not expected to cross-react in patients with CIU. Zembowicz *et al.*⁴² reported that none of 18 subjects with challenge-confirmed NSAID-exacerbated CIU reacted to selective COX-2 inhibitors. Quiralte *et al.*⁴³ conducted single-blind, placebo-controlled oral challenges with rofecoxib in 32 subjects and with celecoxib in 25 subjects; all had a history of NSAID-induced anaphylactoid reactions, including urticaria and angioedema. Both medications were well tolerated in all cases.

Other studies that reported possible cross-reactivity of the COX-2 inhibitors in patients with NSAID-induced cutaneous reactions suffer from one or more methodological flaws. The latter include lack of confirmatory challenges or double-blind method, misinterpretation of probable IgE-mediated reactions, and possible inclusion of patients with AERD.^{44,45}

Celik *et al.*⁴⁶ evaluated the long-term tolerability of COX-2 inhibitors in analgesic-intolerant patients who previously had negative oral challenges to nimesulide, meloxicam, rofecoxib, or celecoxib. Of those patients who had used the recommended COX-2 inhibitor, 89% showed long-term tolerability whereas 11% reported adverse events. Three patients who reported adverse events were rechallenged to the suspected COX-2 inhibitor with negative results. This underscores the importance of confirmatory challenges before attributing NSAID-induced cross-reactivity to COX-2 inhibitors. Although selective COX-2 inhibitors are tolerated by the vast majority of NSAID-allergic subjects, their use in general has been curtailed by their cardiovascular side effects.⁴⁷

NEW CONCEPTS IN BIOLOGICAL AGENTS ALLERGIES AND DESENSITIZATION

Until recently, drug desensitization was limited to penicillin and to a lesser extent antibacterial sulfonamides, aspirin, insulin, heterologous antisera, and a few others. The procedure typically follows a rush protocol and is repeated at every administration unless the drug is being taken daily. As the development and use of biological therapeutic agents have increased, adverse reactions to this class of medication are more commonly encountered. Experience with desensitization to therapeutic biological agents such as pancreatic enzymes and TNF- α inhibitors have been reported. In some reports, desensitization protocols included premedication with antihistamines and corticosteroids to reduce the chance of reactions during the procedure.

Desensitization to Pancreatic Enzyme

Hypersensitivity reactions to pancreatic enzyme preparations are very rare, but we encountered a case that was desensitized successfully.⁴⁸ The patient was a child with cystic fibrosis who initially tolerated Pancrease MT16 (McNeil Pharmaceutical, Raritan, NJ) but later developed vomiting with every ingestion of that preparation. The same symptoms occurred after switching to three other preparations (Ulterase, Scandipharm, Birmingham, AL) Creon 10 (Solvay Pharmaceuticals, Marietta, GA) and Viokase (Robins Co., Richmond, VA). Using double-blind, placebo-controlled titrated oral challenges, vomiting occurred after the ingestion of two pancreatic enzyme preparations tested, but not to placebo. A rapid desensitization protocol was initially attempted using Viokase solution, but was discontinued due to severe vomiting. A slower protocol was designed using Pancrease MT16 starting with one-fourth of a capsule and gradually increased until reaching the therapeutic dose (1 capsule 3 times/day) by day 25. The procedure was successful without any concomitant administration of antihistamines or corticosteroids and the patient continued to take Pancrease MT16 without any reaction.

Desensitization to Anti-TNF- α (Infliximab)

Infliximab, a chimeric monoclonal antibody against TNF- α is being increasingly used to treat Crohn's disease, rheumatoid arthritis, and psoriasis. This chimeric antibody contains ~25% murine sequences and therefore IgE-mediated reactions to the murine protein are possible. Systemic reactions have been reported to occur in 6% of infusions and include both acute reactions and delayed serum sickness-like disease.⁴⁹ Such reactions often result in switching to a less effective therapy. Many patients with mild to moderate acute reactions may tolerate the drug by reducing the rate of infusion and/or premedication with antihistamines,

acetaminophen, and corticosteroids.⁴⁹ The success with such intervention suggests that most reactions to anti-TNF- α are not IgE-mediated.

The effect of immunosuppressive therapy in infliximab infusion reactions was evaluated in the ACCENT 1 study in which 573 patients with Crohn's disease were randomized to infliximab versus placebo infused every 8 weeks for 54 weeks.⁵⁰ The authors reported that concomitant immunosuppressive agents did not significantly affect the development of infusion reactions. However, other studies reported different findings. Baert *et al.*⁵¹ studied 125 patients with Crohn's disease treated with infliximab and evaluated serum concentrations of infliximab and anti-infliximab antibody as well as concomitant medication use. Antibodies against infliximab were detected in 61% of patients. Elevated anti-infliximab concentrations were associated with a higher frequency of infusion reactions (relative risk, 2.4) and predicted a shorter duration of therapeutic response to the drug (35 days versus 71 days). Patients with infliximab infusion reactions had significantly lower infliximab concentrations at 4 weeks postinfusion and had a shorter median duration of clinical response (38.5 days versus 65 days). Concomitant immunosuppressive therapy was associated with reduced formation of anti-infliximab antibodies, which suggests a decreased incidence of infusion reactions.

A similar study involving a predominantly pediatric population was reported by Miele *et al.*⁵² Of 34 patients with inflammatory bowel disease being treated with infliximab, 29 were also receiving immunosuppressive agents. Human antichimeric antibody (HACA) was detected in 12 (35.3%) of 34 patients, and infusion reactions occurred in 8 (23.5%) patients. Patients with HACA had a significantly greater risk of infusion reactions, especially when HACA levels were ≥ 8 $\mu\text{g/mL}$. Concomitant immunomodulatory treatment was associated with a reduced risk of developing HACA and of adverse reactions.

Patients with a severe acute infusion reaction to infliximab, a positive skin-prick test, and elevated HACA may have an immunologic etiology and therefore are unlikely to respond to a slower infusion rate or premedication. To the best of our knowledge, to date, there are two reports of successful desensitization to infliximab in a small number of patients.^{53,54} Recently, we reported a protocol for infliximab desensitization at the 2005 annual meeting of the American Academy of Allergy, Asthma and Immunology.⁵⁵ The protocol included i.v. administration of a starting dose of 0.01 mg with increasing increments every 15 minutes until the therapeutic dose (270–575 mg) is reached over 4–5 hours without any premedication. This protocol was applied to several patients (multiple times at 6- to 8-week intervals) without significant adverse reactions.

CONCLUSIONS

A better understanding of drug pharmacology and disease pathophysiology has led to significant improvement in the management of adverse drug reactions. IVIG has been associated with enhanced healing and improved survival in patients with SJS and TEN. The lack of benefit noted in a few studies should not negate the benefit reported by the vast majority of published studies, especially in this syndrome that has a high mortality and limited therapeutic options.

Patients with allergic reactions to antibacterial sulfonamides generally tolerate non-antibacterial sulfonamides. However, certain patients may have a genetic predisposition to develop multiple drug reactions, including various sulfonamides.

"Cross-reactivity" among several NSAIDs is not IgE mediated but rather represents a pseudoallergic condition caused by inhibition of the COX-1 enzyme. Patients with AERD or NSAID-induced cutaneous reactions can usually tolerate selective COX-2 inhibitors. Subjects with a prior intake of selective COX-2 inhibitors may develop IgE sensitization and react to that drug, which should not be misinterpreted as COX-1 cross-reactivity.

The development of new therapeutic biological agents and their increased use in a number of diseases has resulted in more adverse reactions. In the absence of optimal alternative therapies, desensitization protocols can be developed. Desensitization to pancreatic enzymes and infliximab are examples. More protocols are expected to be developed for other biological therapeutic agents.

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