REVIEW ARTICLE

The complexity of adverse side-effects to biological agents☆

François Aubin a,⁎, Franck Carbonnel b, Daniel Wendling c

a Université de Franche Comté, EA3181, et Centre Hospitalier Universitaire, Service de Dermatologie, Besançon, France
b Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire de Bicêtre, Assistance Publique-Hôpitaux de Paris, Université Paris Sud, France
c Service de Rhumatologie, Centre Hospitalier Universitaire et Université de Franche Comté, Besançon, France

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Side effects;
Adverse events

Abstract
Whereas adverse effects induced by xenobiotics are mainly linked to the pharmacological effect, the adverse side-effects induced by biological agents (BA) are often target-related and linked to the biological consequences of their action. Based on these differences, an original classification of the adverse effects has been proposed. Five types of adverse effects induced by BA are described (α, β, γ, δ, and ε). This classification provides a very useful scheme for a better understanding of these adverse effects. This approach should help to better characterize the pathogenic mechanisms involved and to optimize their management. Healthcare professionals should be aware of the specific risks related to this relatively new class of drugs. Close monitoring of these BA is therefore recommended.

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⁎ Corresponding author at: Service de Dermatologie, 2 Place Saint-Jacques, 25030 Besançon cedex, France.
E-mail address: faubin@chu-besancon.fr (F. Aubin).

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1. Introduction

For about 10 years, biological agents (BA), including cytokines, monoclonal antibodies and fusion proteins are widely used in various autoinflammatory and immune diseases and tumours. Besides, they may induce new side-effects that require specific knowledges as they differ from common side-effects induced by conventional drugs.

Although very heterogeneous, adverse side-effects induced by traditional drugs may be classified into 5 types.1,2 Type A reactions are the most frequent and correspond to the pharmacological activity of the drug. They are thus predictable. Type B reactions are immune-mediated and are thus not predictable. They include immediate and delayed hypersensitivity reactions. Type C and D reactions involve short-term and long-term toxicities. They are linked to the chemical structure of the drug and its metabolism (i.e., hepato- and nephrotoxicity). Type E reactions occur after withdrawal of the drug.

In contrast, BA demonstrate clear differences with traditional drugs in terms of chemistry, mode of action, metabolism and immunogenicity (Table 1). Contrary to traditional chemically synthetized drugs, BA are large protein complexes, which can be obtained from cultures of bacteria, yeast, insects, plants, or mammalian cells engineered with the gene of interest or can be purified from natural sources (i.e. clotting factors). Manufacturing quality is a significant issue relative to the toxicity of BA. The development of recombinant technology represented the single biggest advance leading to humanized products with minimal or no contaminants in comparison to products purified from animal tissues. Nevertheless, the type of manufacturing process including choice of cell type, culture medium, and purification method can result in changes to the protein.

Table 1 Comparison of traditional drugs and biological agents (6,37): MW: molecular weight.

<table>
<thead>
<tr>
<th>Traditional drugs</th>
<th>Biological agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule (MW&lt;1 kDa)</td>
<td>Large complex molecules (MW&gt;1 kDa)</td>
</tr>
<tr>
<td>Synthesized chemicals (xenobiotics)</td>
<td>Structurally similar to autologous proteins</td>
</tr>
<tr>
<td>Metabolized to active and inactive products</td>
<td>Produced with molecular genetic technique and purified from engineered cells</td>
</tr>
<tr>
<td>Cytochrome P450 involvement</td>
<td>Catabolized to endogenous amino acids</td>
</tr>
<tr>
<td>Multiple drug interactions</td>
<td>Cytochrome P450 independent</td>
</tr>
<tr>
<td>Oral administration possible</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Linear dose–response</td>
<td>Oral administration not possible</td>
</tr>
<tr>
<td>Pharmacological effect</td>
<td>Non linear dose–response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Reactions related to cytokine and cytokine released syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Reactions include both immediate and delayed hypersensitivity reactions.</td>
</tr>
<tr>
<td>β</td>
<td>Reactions are related to immune imbalance syndrome.</td>
</tr>
<tr>
<td>γ</td>
<td>Cross-reactions related to the expression of the same antigen on different tissue.</td>
</tr>
<tr>
<td>δ</td>
<td>Reactions are non-immunological side-effects (new and original unexpected functions of biological agent).</td>
</tr>
</tbody>
</table>

Because of their structure (large molecules) and origin (foreign non-self proteins), BA are intrinsically immunogenic, and may induce anti drug antibodies, which may be related to drug reactions at one hand3 and reduced efficacy at the other hand.4

Whereas adverse side-effects induced by xenobiotics are mainly linked to the pharmacological effect, the adverse side-effects induced by BA are often target-related and linked to the biological consequences of their action.5 Based on these differences, Pichler6 proposed an original classification of the adverse side-effects induced by BA. As for xenobiotics, adverse drug reactions of BA are classified by their pathomechanism. Five types of adverse side-effects were described (Table 2). Types α, β, γ, and δ reactions may be related to different aspects of the immunotoxicity induced by BA, including immunostimulation, immunodeviation (immunosuppression and autoimmunity), immunogenicity (hypersensitivity reactions), cross-reactivity and other non-immunological adverse effects.7,8

Type α reactions are induced by high cytokine levels. The cytokine release syndrome observed during IFN or IL-2 treatment includes fever, asthenia, arthragia, headache, myalgia, gastrointestinal symptoms (nausea, vomiting, diarrhoea). Cutaneous eruption mimicking a Sweet’s syndrome or acute febrile neutrophilic dermatosis (Fig. 1) has also been described after administration of granulocyte colony stimulating factor that causes increased neutrophil proliferation and differentiation.9 The term cytokine storm have been used to describe a multi-organ dysfunction syndrome induced by an inappropriate generalized inflammatory response.10 The release of high levels of pro-inflammatory cytokines including IL-1β, TNF-α, IFN-α/β/g, IL-6 and IL-8, and complement activation are considered to be the main underlying mechanisms.7

Type β reactions involve hypersensitivity reaction linked to the immunogenicity of BA. Although mouse and chimaeric antibodies are more immunogenic, humanized and fully human antibodies can still elicit an anti-idiotypic immune response.11 Development of antibodies to BA or anti-drug antibodies (ADA) depends on several factors including the immunogenicity of the protein (mouse vs human), the route of administration (subcutaneous versus intravenous), treatment regimens (intermittent versus continuous), and the concomitant use of immunosuppressive drugs.12 ADA development is associated with decreased therapeutic effectiveness and, in many cases, with the occurrence of immunoaллерgic adverse events. However, there is no clear evidence that ATIs have an
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impact on efficacy or safety, nor a need to measure or prevent them in clinical practice.13

Both immediate and delayed-type reactions may occur.14 Immediate reactions occur in 3–5% of patients treated with chimaeric BA. They often occur at the site of subcutaneous injection (Fig. 2) leading to a local flare and wheal reaction. Such reactions can disappear when the treatment is continued, which suggests that tolerance may be induced. These reactions are not dose-dependent, they can relapse at prior injection sites (recall phenomenon). Local reactions are mostly not IgE-mediated and may involve non-immunologic irritation to BA or to its excipients.14

Acute systemic reaction with fever, urticaria and anaphylaxis may also occur, i.e. during infliximab, rituximab, omalizumab or natalizumab infusions. These reactions commonly/usually appear rapidly within minutes and last for 30 to 60 min. No correlation between the atopic status of the patient and the incidence of hypersensitivity reactions has been demonstrated with different TNF-alpha blocking agents.15

The majority are mild reactions and can be reduced by slowing the infusion rate and giving antihistamines and paracetamol. More severe systemic reaction may require corticosteroids.14,16 Although premedication is often routinely given before infusion consisting of paracetamol, antihistamines and/or corticosteroids, there are no solid evidence that prophylactic medication can prevent infusion reactions.12,14 Desensitization protocols have also been proposed.17

The pathomechanisms of infusion reactions remain unclear. The immunogenicity of BA along with the formation of ADA, the release of high level of pro-inflammatory cytokines or histamine and complement activation have been suggested. Although the formation of ADA may be reduced by the concomitant use of immunosuppressive drugs,12,18 there is no clear evidence for prevention in clinical practice.3,13

Delayed reactions occur >6 h after treatment and are immunoglobulin-mediated. Formation of IgG antibodies against the BA may occur rather frequently, up to 68% of patients treated with the chimaeric antibody infliximab.19 However, these antibodies anti-BA are not systematically associated with symptoms and the most frequent consequence is inactivation of the BA and reduction of efficacy.20 Formation of antibodies may induce the activation of complement cascade through immune complexes formation resulting in serum sickness, vasculitis (Fig. 3) and nephritis.21 The sensitization and antibodies formation to anti-TNF agents can be reduced by the co-medication with methotrexate.12,19

Type γ reactions are related to immunodeviation, including immunosuppression and autoimmunity through immune or cytokine imbalance. Tests to detect hypersensitivities like skin tests or in vitro detection of antibodies are negative. BA may induce an immunodeficiency which is beneficial for the disease but deleterious for the optimal and rapid control of infection or tumoral cells. Anti-TNF-α agents are very effective for psoriasis rheumatoid arthritis, ankylosing spondylitis and Crohn’s disease but may be associated with severe infections such as herpes zoster,22 tuberculosis or listeriosis. The monoclonal antibodies natalizumab, efalizumab, and rituximab (used for the treatment of multiple sclerosis, psoriasis, haematological malignancies, Crohn’s disease, and rheumatic diseases) have been associated with progressive multifocal leukoencephalopathy caused by reactivation of the polyomavirus JC.23

In addition to the infectious risk, the delayed risk of cancer is still an important issue and may be related to the immunodeficiency induced by BA. However, many biological agents have also proved their efficiency in various tumours as their direct and targeted effects makes them superior to conventional cytotoxic drugs. Immunosuppression with TNF inhibition increases the risk for certain malignancies.24–26

Figure 1  Sweet’s syndrome or acute febrile neutrophilic dermatosis after the administration of filgrastim (type α reaction).

Figure 2  Local reaction (type β) after etanercept subcutaneous injection.

Figure 3  Cutaneous vasculitis (type β) during adalimumab treatment in Crohn’s disease.
including lymphoma and non-melanoma skin cancer, but data for actual rates, however, are confounded by past or concomitant use of immunosuppressive agents.27–29 In a recent meta-analysis assessing the risk of lymphoma in 8905 Crohn’s disease patients treated with anti-TNF agents and immunosuppressive drugs, Segel et al.30 observed a significant increase of standardized incidence ratio in these patients when compared with the expected rate derived from the Surveillance, Epidemiology, and End Results database. However, this increase was not significantly different from those observed in patients receiving immunosuppressive drugs alone. In a meta-analysis including 5356 patients with Crohn’s disease, anti-TNF therapy did not increase the risk of death, malignancy, or serious infection.31 However, the follow-up was not more than one year. Altogether, these different studies suggest that although the risk of cancer associated with chronic use of anti-TNF therapy as sole therapy has not been assessed, the risk-to-benefit profile of the TNF-alpha inhibitors in adult patients appears to be favorable.32 Larger, long-term studies with appropriate control groups will be necessary to fully assess the risk of cancer.

BA may also unmask a pre-existing or cause an cytokine imbalance resulting in autoimmunity and auto-inflammatory syndrome. Lupus-like syndrome, systemic sclerosis, thyroiditis, hepatitis nephritis, Guillain-Barré syndrome, and alopecia areata have been reported with anti-TNF-a agents.21,33 Paradoxical adverse side-effects have been reported with TNF antagonists. They correspond to the occurrence during anti-TNF treatment of an unexpected pathological condition that usually responds well to this therapeutic class of drug. Paradoxical psoriasis-like eruptions (Fig. 4),34 vasculitis, and even colitis35 have been described and linked to an increased production of IFN-a36 and an increase of Th17 function along with a reduction of regulatory T cells.37,38 Autoinflammatory or allergic disease (atopic dermatitis) has been described with anti-TNF-a39,40 suggesting a shift of the Th1-Th2 balance and an increase of IL-17 production.41 The inhibition of suppressive function of activated CTLA-4+ T cells by ipilimumab may also lead to autoimmunity and autoinflammatory colitis.42

Type δ cross-reactions are related to the co-expression of the target antigen on both pathologic and normal tissues. Inhibitors of epidermal growth factor receptor (EGFR) are used to treat various tumours and induce acneiform eruptions (Fig. 5).43 Indeed, EGFR is expressed by various carcinoma and is also involved in cutaneous homeostasis.

Type ε reactions are related to new and unexpected physiological functions of BA revealed by the in vivo use in humans. Neuropsychiatric adverse effects of IFN-a44,45 and aggravation of heart failure by anti-TNF-a agents46 may represent such type ε reactions.

The use of BA as a new alternative treatment for chronic autoinflammatory and immune diseases and cancer is expanding worldwide and new adverse side-effects are becoming increasingly recognized. However, these BA are so beneficial that adverse effects should not prevent their use. The classification in 5 types proposed by Pichler6 and discussed by Descotes and Gouraud7 provides a very useful scheme for a better understanding of these adverse effects (Table 3). This approach should help to better characterize

Figure 4  Paradoxical psoriasiform eruption (type γ) during adalimumab treatment in rheumatoid arthritis.

Figure 5  Acneiform eruption (type δ reaction) during cetuximab treatment in head and neck.
23% of BA approved have had at least one safety-related event. Since 1995, healthcare professionals should be aware of the specific adverse effects induced by the main biological agents used for inflammatory bowel disease.

### Table 3

<table>
<thead>
<tr>
<th>Biological agent</th>
<th>Adverse effect</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Acute HSR (local and systemic)</td>
<td>Type beta reaction</td>
</tr>
<tr>
<td></td>
<td>Delayed HSR (serum sickness disease)</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Paradoxical adverse effects: vasculitis, colitis, psoriasis-like eruption, etc.</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td></td>
<td>Autoimmunity: lupus, hepatitis, thyroiditis, etc.</td>
<td>Type epsilon reaction</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Acute HSR (local and systemic)</td>
<td>Type beta reaction</td>
</tr>
<tr>
<td></td>
<td>Delayed HSR (serum sickness disease)</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td>Anti-alpha-4 integrin Natalizumab</td>
<td>Infection: progressive multifocal leukoencephalopathy</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td></td>
<td>Autoimmunity: hepatitis, thyroiditis</td>
<td>Type gamma reaction</td>
</tr>
<tr>
<td>Anti-IL12/anti-IL23 Ustekinumab</td>
<td>Delayed HSR (serum sickness disease)</td>
<td>Type beta reaction</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Type gamma reaction</td>
</tr>
</tbody>
</table>

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2. Conflict of interest

None declared.

References


