

The Safety of Therapeutic Monoclonal Antibodies: Implications for Cancer Therapy Including Immuno-Checkpoint Inhibitors

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Summary

Monoclonal antibody-based treatment of cancer has been established as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumors. In addition to targeting cancer antigens antibodies can also modulate immunological pathways that are critical to immune surveillance. Antibody therapy directed against several negative immunologic regulators (checkpoints) is demonstrating significant success in the past few years. Immune checkpoint inhibitors, ipilimumab, pembrolizumab and nivolumab, have shown significant clinical benefit in several malignancies and are already approved for advanced melanoma and squamous NSCLC. Based on their mechanism of action, these agents can exert toxicities that are unlike conventional cytotoxic chemotherapy, whose nature is close to autoimmune diseases - immune related adverse events (irAEs). In this review we focus on the spectrum of irAEs associated with immune checkpoint antibodies, discussing the pharmacological treatment strategy and possible clinical impact.

Key words

Cancer treatment • Monoclonal antibodies • Immune checkpoint inhibitors • Immune related adverse events

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Monoclonal antibodies in cancer

Monoclonal antibodies (mAbs) are a rapidly growing class of human therapeutics representing

approximately 25 % of drugs under development (Datamonitor: Pipeline insights 2009). By 2014, 34 therapeutic mAbs are predicted to be on the market for treating cancer, autoimmune diseases, and infectious diseases (Datamonitor: Pipeline insights 2009). Since their discovery in 1975, mAbs have been described as "magic bullets" with the potential to seek out and bind targets with high affinity and specificity (Kohler *et al.* 1975). Cancer diseases are one of the major groups where monoclonal antibodies are used in clinical practice. There have been twelve antibodies that have received approval from the FDA for the treatment of a variety of solid tumors and hematological malignancies in 2014 (Scott *et al.* 2012). In addition, there are a large number of additional therapeutic antibodies that are currently being tested in early- and late-stage clinical trials. The most common type of mAbs used to treat cancer are "naked mAbs". Most naked mAbs attach to antigens on cancer cells, but some work by binding to antigens on other, non-cancerous cells, or even free-floating proteins. We can simplify three major mechanism of actions of naked mAbs. One principle is boosts a person's immune response against cancer cells by attaching to them and acting as a marker for the body's immune system to destroy them. An example is alemtuzumab, which binds to the CD52 antigen on lymphocytes and is used to treat some patients with chronic lymphocytic leukemia (CLL). Another naked mAbs work mainly by attaching to and blocking antigens on cancer cells that help cancer cells grow or spread. For example, trastuzumab is an antibody against the HER2 protein. Currently the most researched mAbs are naked mAbs which boost the immune response

by targeting immune system checkpoints like anti-CTLA-4 monoclonal antibody ipilimumab or nivolumab and pembrolizumab targeting programmed cell death 1 receptor (PD-1). Adverse effects of this immune checkpoint inhibitors will be discussed in this review in more detail.

In cancer therapy apart from the naked Mabs we can use also conjugated monoclonal antibodies, mAbs joined to a chemotherapy drug or to a radioactive particle. Conjugated mAbs are also sometimes referred to as tagged, labeled, or loaded antibodies. Ibritumomab tiuxetan is an example of a radiolabeled mAb. Antibody-drug conjugates (ADCs) like brentuximab vedotin targets the CD30 antigen, trastuzumab emtansine (also called TDM-1) is an antibody that targets the HER2 protein attached to a chemo drug called DM1. It's used to treat some breast cancer patients whose cancer cells have too much HER2. Bispecific monoclonal antibodies are made up of parts of 2 different mAbs, meaning they can attach to 2 different proteins at the same time. An example is blinatumomab, which is used to treat some types of acute lymphocytic leukemia (ALL). One part of blinatumomab attaches to the CD19 protein, which is found on some leukemia and lymphoma cells. Another part attaches to CD3, a protein found on immune cells called T cells. By binding to both of these proteins, this drug brings the cancer cells and immune cells together, which is thought to cause the immune system to attack the cancer cells.

Compared with chemotherapy drugs, monoclonal antibodies tend to have fewer serious side effects, however, as with all agents, administration of mAbs should be associated with adverse events (AEs) as a result of enhancing/inhibiting the activity of the target molecule on the target tissue, or due to interactions of the mAb with target molecules on tissues other than the intended ones (Catapano *et al.* 2013).

Classification of adverse effects of biological agents

Traditionally, adverse reactions should be subclassified according to their action (Naisbitt *et al.* 2000) (Table 1): so-called type A reactions correspond to the pharmacological activity of the drug, and are thus predictable (Hoigne *et al.* 1993). About 16 % of side effects are type B reactions (Naisbitt *et al.* 2000), which are not related to the pharmacological activity of the drug and are nonpredictable. The majority of type B reactions are immune-mediated side-effects like hypersensitivity reactions. Types C, D, and E are not mechanisms but characteristics of their manifestations; they are not referred to frequently in the literature. The letter C refers to continuous, chronic. Type D refers to delayed in appearance, making them difficult to diagnose. Type E refers to end of use, F means failure of therapy (Edwards *et al.* 2000).

Table 1. Classification of adverse drug reactions (Naisbitt *et al.* 2000).

Type A (augmented) reactions	Predicted from the known pharmacology of the drug. These reactions are dose-dependent: examples are bleeding with anticoagulants
Type B (bizarre) reactions	Reactions are not predicted from the known pharmacology of the drug. They appear (but actually are not) relatively dose-independent, as very small doses might already elicit symptoms. They include immune-mediated side-effects like maculopapular exanthema, but also other hypersensitivity reactions, like aspirin-induced asthma
Type C (chronic) reactions	Which are related to the chemical structure and its metabolism, e.g. paracetamol hepatotoxicity
Type D (delayed) reactions	Which appear after many years of treatment, e.g. bladder carcinoma after treatment with cyclophosphamide
Type E (end of treatment) reactions	Occur after drug withdrawal, e.g. seizures after stopping phenytoin

Biological agents differ from most drugs as they are not small chemical compounds (xenobiotics) but are proteins produced in a way to make them as similar to human proteins as possible. They are not metabolized like

drugs but are processed like other proteins, with the differences in pharmacokinetic as well as pharmacodynamic properties. Thus, adverse reactions to biological agents might differ from those elicited by

classical drugs. More appropriate classification of mAbs adverse effects is a subclassification published by Pichler *et al.* (2006) based on mechanism of action and structure, as illustrated in Figure 1. To distinguish it from the classification of side-effects to chemicals/drugs (Table 1), the Greek alphabet is used for the five types (type α , β , γ , δ and ϵ). Type α (high cytokine and cytokine release syndrome) are side-effects connected to the systematic application of cytokines in relatively high doses or to high concentrations of cytokines released into the circulation (Vasquez *et al.* 1995). Type β reactions can be termed as hypersensitivity. Thereby basically three forms of allergies can be differentiated: IgE-, IgG- and T cell-mediated reactions. Type γ immune (cytokine) imbalance

syndromes have immunological features, but cannot be explained by high cytokine levels or typical hypersensitivity reactions. As illustrated in Figure 1, these reactions can be further subdivided in, impaired functions, and unmasking or causing an immune imbalance leading to autoimmune, auto-inflammatory or allergic reactions. Type δ (cross-reactivity) might be that antibodies generated to an antigen expressed on tumour cells might also cross-react with normal cells, which express this structure as well, albeit to a lower degree (Perez-Soler *et al.* 2005). Type ϵ (non-immunological side-effects) may elicit symptoms not directly related to the immune system, sometimes revealing unknown functions of the biological agents given or targeted.

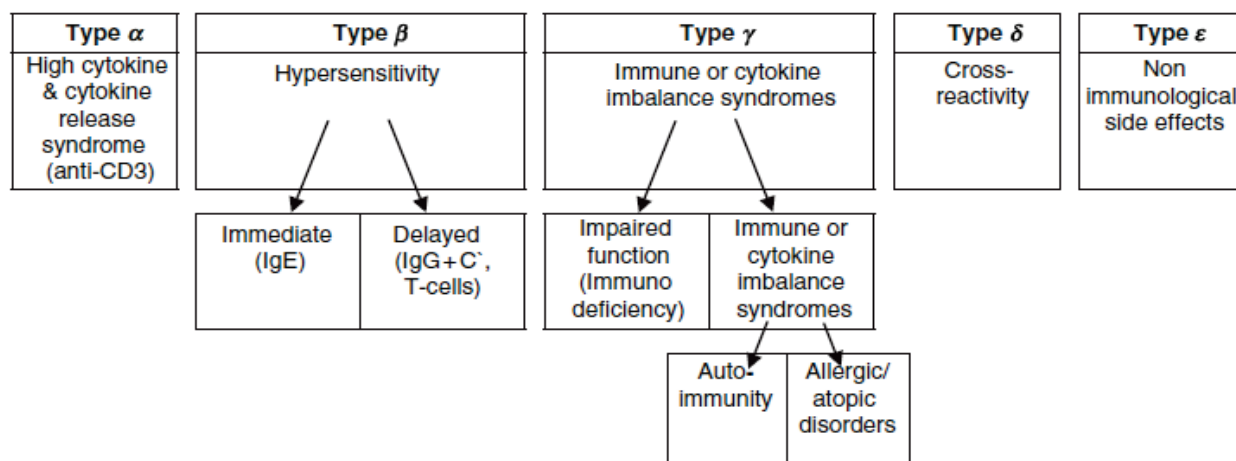


Fig. 1. Type of adverse effects of biological agents. (Pichler 2006).

Immuno-checkpoints inhibitors and immune related adverse events (irAEs)

Cancer therapy based on monoclonal antibodies against checkpoints of immune reaction is today considered a breakthrough method in oncology. Results with the anti-CTLA-4 (cytotoxic T lymphocyte antigen-4) antibody ipilimumab in the treatment of advanced malignant melanoma have represented a revolution in anti-tumour therapy and been a catalyst for developing new antibodies focusing on other control molecules (checkpoints) (Lakomy *et al.* 2015) What is especially worth mentioning in this context are the antibodies against programmed cell death receptor (PD-1) – nivolumab and pembrolizumab and against its ligand (PD-L1), BMS-936559, MPDL3280A or lambrolizumab ((Weber *et al.* 2015, Hamid *et al.* 2013)). The development and use of immune therapy have achieved their greatest progress so far in advanced melanoma, but

soon we will be similarly treating non-small-cell pulmonary carcinoma and other tumour types.

These antibodies prevent an inhibition of interaction between PD-1 and PD-L1/L2, on the other hand cause secondary potentiation of the effector component of immunity on the “peripheral” level directly in the tumour tissue. Break of tolerance towards the tumour may, however, be accompanied by unwanted break of tolerance towards “normal tissues”, which leads to adverse reactions whose nature is close to autoimmune diseases – immune related adverse events (irAEs). IrAEs include dermatologic, GI, hepatic, endocrine, and other less common inflammatory events. Because irAEs likely arise from general immunologic enhancement, temporary immunosuppression with corticosteroids, tumor necrosis factor α antagonists or other agents is often necessary and should follow established algorithms (Postow *et al.* 2015). Due to the high frequency of irAEs with the risk of life-threatening complications, sufficient education of

patients, their family members and medical specialists is necessary. Warnings and recommendations have been prepared about how to proceed suspected irAEs. Early commencement of immunosuppressive therapy with corticosteroids is the key step towards management of the incident, reduction of morbidity and potentially also mortality. If corticoids are not sufficiently effective, other immunosuppressants are added, such as infliximab or mycophenolate mofetil (Lakomy *et al.* 2015).

Side effects of ipilimumab

Ani-CTLA-4 monoclonal antibody ipilimumab was the first immune checkpoint receptor used in daily clinical practice. The frequency of adverse effects of ipilimumab is relatively high; in a pre-authorization study of the dose of 3 mg/kg it ranged between 80 – 90 %. Luckily the toxicity was mild to moderate in the vast majority of the cases (grade 1 and 2 toxicity). Serious (grade 3) and life-threatening (grade 4) toxicity pursuant to NCI-CTCAE v3.0 (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0) was reported for about 20 – 25 % of the study population (Hodi *et al.* 2010). Adverse effects may already occur in the course of or after the infusion (nausea, vomiting, febrility, pain and vertigo, rash and pruritus), but these reactions are singular and mostly non-serious. The general recommendation is to suspend the infusion until symptoms retreat, with potential administration of antihistaminics or antipyretics, and subsequently to restart at a slower (about half) speed with patient monitoring (Fecher *et al.* 2013). Premedication with antihistaminics or antipyretics before the following administrations is recommended for consideration in those cases. In the case of serious adverse reaction of levels 3 and 4 (bronchospasm, hypotension, anaphylaxis) the procedure is identical to other hypersensitivity reactions, with the permanent discontinuation of therapy recommended. The irAEs are a bigger concern, though, as they are most common and grow with the dose. In the case of the dose of 3 mg/kg they appear in up to 60 % of patients, while severe irAE toxicity of levels 3 and 4 has been reported for 10 – 15 % of the study subjects (Hodi *et al.* 2010, Wolchok *et al.* 2010). The most frequent irAEs include dermal toxicity (rash, pruritus), enterocolitis and diarrhea, endocrinopathy (hypophysitis, thyroiditis) and liver test elevation. The immune system may, however, attack any part of the anatomy (heart, lungs, kidneys, nervous system, eyes, hematopoietic system etc.). Biopsy

then most often reveals tissue infiltration with T lymphocytes or with neutrophils (Fecher *et al.* 2013). Over time, we can first expect dermal toxicity (after three weeks), followed by colitis and diarrhea (after five weeks), hepatic toxicity (after 6 – 7 weeks) and finally endocrinopathy (after 7 – 8 weeks from therapy commencement) (Weber *et al.* 2012). We should also remember that IrAEs may, however, also appear a couple of weeks or months after therapy completion. The text below will deal with the most frequent irAEs and how to address them.

Immune-conditioned dermal toxicity

Dermal toxicity is one of the most common irAEs (40 – 45 %) usually first occurring after week 3 of therapy and culminating in week 6 (Lakomy *et al.* 2015, Hodi *et al.* 2010, Weber *et al.* 2012). This is mostly level 1 toxicity (affecting <10 % of the body surface) or toxicity level 2 (with an effect on between 10 and 30 % of the body surface). Severe toxicity (levels 3 and 4) is luckily rare, only ranging between 1 – 2 % in the pre-authorization study. Usual manifestations include maculopapular exanthema (20 %) and/or pruritus (25 %). Another manifestation may be vitiligo, which is rather cosmetic issue, but the patient must be educated about protection against UV radiation. Blisters are already a manifestation of a severe reaction. Stevens-Johnson syndrome and toxic epidermal necrolysis occur in <1 % patients and are a reason for permanent discontinuation of therapy.

Immune-conditioned colitis and diarrhea

Diarrhea induced by ipilimumab is another of the most common autoimmune-conditioned adverse reactions. This effect appears after week 5 of therapy. In the case of an ipilimumab dose of 3 mg/kg, this AE occurs in about 30 % patients, and incidence rises with the dose – 44 % at 10 mg/kg i.v. (Hodi *et al.* 2010, Weber *et al.* 2012). Severe diarrhea or colitis levels 3 or 4 occur in the case of a 3 mg/kg dose in about 5 – 8 % of patients, colitis most often affecting the descending colon (Wolchok *et al.* 2010). A big threat is potential intestinal perforation, with potential fatal consequences.

Prophylactic administration of oral corticoids (budesonide) did not change the incidence of diarrhea (Weber *et al.* 2009). The so far published results suggest that immunosuppressive corticoid therapy administered in

the course of the immunotherapy does not substantially affect the therapeutic effect of ipilimumab (Weber *et al.* 2009, Harmankaya *et al.* 2011).

Immune-conditioned hepatic toxicity

Hepatic toxicity caused by ipilimumab, even though rarer in comparison to the previously mentioned immune-conditioned adverse effects, may also represent a life-threatening reaction. The onset of this irAE usually occurs after week 6 of ipilimumab therapy, becoming very rare after week 14 (Weber *et al.* 2012). If all recommendations for diagnosis and treatment are observed, the prognosis for patients with this type of irAE is excellent; the liver test results usually normalize very quickly after commencement of the appropriate therapy – in about two weeks (Della Scarpata *et al.* 2014). A patient with hepatic toxicity may be asymptomatic (laboratory results usually show elevated ALT and/or AST and/or bilirubin), but frequent complaints include febrility, fatigue, nausea, jaundice, changed stool color or urine colour, and sometimes pruritus. Patient examination must include taking a careful medical history to exclude other causes – fungi, alcohol, contact with chemicals or the effect of concurrent medication (such as paracetamol and others). Clinical examination may reveal, in addition to icterus, also hepatomegaly, the patient may be exhausted, or the find may be completely negative. An infectious cause must always be excluded in level 2 and higher of hepatic toxicity, and antibodies against nuclear antigen and mitochondrial antigen must be sampled (ANA, SMA). Exclusion of progression of the malignant disease by imaging methods is also necessary. In the case of level 3 and 4 toxicity, liver biopsy is to be considered (finds typical of hepatic toxicity include infiltration of the liver parenchyma with T lymphocytes, sometimes with necrosis of hepatocytes) (Lakomy *et al.* 2015).

Immune-conditioned endocrinopathy

Like the immune-conditioned hepatopathy endocrinopathy is also less frequent than dermal or gastrointestinal toxicity, but again represents a potentially life-threatening condition. The deceptiveness of endocrinopathy lies in its late onset (7–8 weeks after ipilimumab therapy commencement, with the highest incidence between weeks 12 and 24), and in the fact that, unlike hepatic toxicity, the probability of occurrence does

not decrease in time from completion of therapy; instead, the appearance of the curve is rather like a plateau (Weber *et al.* 2012).

Possible endocrinopathies include hypopituitarism (with or without hypophysitis), hypofunction of the adrenals, hypo- or hyperfunction of the thyroid gland and hypofunction of the gonads. In the case of a suspected adverse effect of this kind, the medical history of the patient is again important (incidence of endocrinopathies in the patient's personal and family history), the patient may complain of non-specific symptoms such as fatigue, weakness, febrilia, abdominal pain, vomiting, diarrhea, headaches or sensory disorders. Clinical warning symptoms include signs of dehydration, hypotension or other signs of commencing systemic inflammatory response syndrome. Laboratory examinations, apart from basic internal environment parameters (often hyperkalemia, hyponatremia and hypoglycemia) and blood count, include endocrinopathy screening: sampling of free T3 and T4, TSH, antibodies against thyroidal peroxidase – anti TPO, morning serum cortisol, levels of corticotropin (ACTH), and in males testosterone levels, and in females FSH and LH levels. For differential diagnosis, an ACTH stimulation test may be considered. Indicated imaging methods include MRI of the brain, with a focus on hypophysis and also on the exclusion of brain metastases. It must be mentioned at this point, that there does not exist any general consensus about the therapy and monitoring, and the literature shows conflicting data on the therapy of this adverse effect and the possibility of returning to ipilimumab therapy (Weber *et al.* 2012, Della Scarpata *et al.* 2014, O'Day *et al.* 2010). Repeated consultations and cooperation with an endocrinologist are a priority. If corticoids need to be administered (toxicity levels 3 and 4), then corticoids with mineralocorticoid activity are preferred with slow discontinuation (Lakomy *et al.* 2015).

Less frequent immune-conditioned adverse effects

Other possible, although rare (less than 1 % of cases), immune-conditioned adverse effects of ipilimumab include: meningitis, uveitis, pneumonitis, pancreatitis, pericarditis, myocarditis, nephritis, various angiopathies, hemolytic anemias, thrombocytopenia etc. Straightforward therapeutic procedures are not known, where such adverse effects occur therapy is managed like it is for other autoimmune diseases with corticoids as the

therapy of choice. Generally, level 3 and 4 toxicity is a reason for discontinuing ipilimumab therapy. Details are in the ipilimumab SmPC (EMA 2012).

Immune-conditioned adverse effects of anti-PD-1/PD-L1 antibodies and their combination with ipilimumab

Toxicity of these antibodies is generally lower than of ipilimumab Topalian *et al.* 2012, Wolchok *et al.* 2015). Severe dermal toxicity levels 3 and 4 are exceptional (2 %). Also, level 3 or 4 diarrhea is uncommon (1–2 %), as is hepatic toxicity (below 3 %) and severe endocrinopathy (<1 %). Unlike ipilimumab, pneumonitis occurs more often after anti-PD-1 antibodies (<5 %). Therapy of severe pneumonitis is again based on corticoids in high doses (methylprednisolone 2 mg/kg i.v. 1–2 times daily) or infliximab. Other toxicities are sporadic, but cannot be neglected either. The principles of therapy of irAEs caused by anti-PD-1/PD-L1 antibodies are the same as with ipilimumab. A considerably higher incidence of irAEs has been described in reports from studies of combinations of anti-PD-1 and anti CTLA-4 antibodies (nivolumab + ipilimumab). Here the occurrence of severe irAEs of levels 3 and 4 ranged around 50 %, with significant representations of gastrointestinal toxicity (15 %) and hepatic toxicity (19 %). A number of these severe toxicities, however, only met the laboratory criteria NCI-CTCAE (such as the elevation of amylase and lipase without clinical signs of pancreatitis). The combination resulted in no new toxicity (Wolchok *et al.* 2015).

Conclusions

The development of immune checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) has significantly improved the treatment of a variety of cancers. Although these agents can lead to remarkable responses, their use can also be associated with unique adverse effects. The spectrum of AEs associated with

immune checkpoint antibodies are termed immune-related AEs (irAE's). The underlying pathophysiology relates to the immune-based mode of action of these agents, leading to T-cell inflammatory infiltration of solid organs, and increased serum inflammatory cytokines. IrAEs are frequent side effects of checkpoint inhibitors, they are possibly life-threatening and there is no known predictive biomarker for their occurrence. The most frequent irAEs include dermal toxicity (exanthema, pruritus), GIT toxicity (diarrhea, colitis), endocrine toxicity (hypopituitarism, hypophysitis, hypothyreosis, adrenal insufficiency), liver toxicity (elevation of transaminase, hepatitis), and in connection with anti-PD-1 antibodies, pneumonitis. IrAEs have their onset and duration (kinetics) well described, but since they can even occur several months after therapy completion (endocrinopathy), the safe interval after therapy completion is not known. Incidence of irAEs is higher for ipilimumab (dose-dependent) in comparison to anti-PD-1/PD-L1 antibodies, and even higher for the combination of ipilimumab and nivolumab. Retreat of toxicity may be slower in the case of anti-PD-1/PD-L1 antibodies; therefore long-term follow up is recommended (Weber *et al.* 2015). The important is the early medication of immunosuppressant with corticoids and their slow discontinuation, if the corticoids show insufficient or no effect, other immunosuppressants must be prescribed. These recommendations for therapy of irAEs are universal for all checkpoint inhibitors, although they are mainly based on experience from clinical studies with ipilimumab. New adverse effects may occur with the introduction of new antibodies and their combinations. The success of therapy with checkpoint inhibitors is conditional not only upon the erudition of the clinician, but also upon having an educated and cooperating patient (Lakomy *et al.* 2015).

Conflict of Interest

There is no conflict of interest.

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