The Oncologist®

New Drug Development and Clinical Pharmacology

Antidrug Antibody Formation in Oncology: Clinical Relevance and Challenges

Emilie M.J. van Brummelen,[a,*] Willeke Ros,[a,*] Gertjan Wolbink,[c,d] Jos H. Beijnen,[b,e] Jan H.M. Schellens[a,e]

Departments of [a]Clinical Pharmacology and [b]Pharmacy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [c]Immunopathology, Sanquin Research, Amsterdam, The Netherlands; [d]Reade Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands; [e]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

*Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immunogenicity • Antidrug antibody • Cancer • Oncology • Pharmacokinetics • Toxicity • Efficacy • Clinical relevance • Detection assays

Abstract

In oncology, an increasing number of targeted anticancer agents and immunotherapies are of biological origin. These biological drugs may trigger immune responses that lead to the formation of antidrug antibodies (ADAs). ADAs are directed against immunogenic parts of the drug and may affect efficacy and safety. In other medical fields, such as rheumatology and hematology, the relevance of ADA formation is well established. However, the relevance of ADAs in oncology is just starting to be recognized, and literature on this topic is scarce. In an attempt to fill this gap in the literature, we provide an up-to-date status of ADA formation in oncology. In this focused review, data on ADAs was extracted from 81 clinical trials with biological anticancer agents. We found that most biological anticancer drugs in these trials are immunogenic and induce ADAs (63%). However, it is difficult to establish the clinical relevance of these ADAs. In order to determine this relevance, the possible effects of ADAs on pharmacokinetics, efficacy, and safety parameters need to be investigated. Our data show that this was done in fewer than 50% of the trials. In addition, we describe the incidence and consequences of ADAs for registered agents. We highlight the challenges in ADA detection and argue for the importance of validating, standardizing, and describing well the used assays. Finally, we discuss prevention strategies such as immunosuppression and regimen adaptations. We encourage the launch of clinical trials that explore these strategies in oncology. ***The Oncologist*** 2016;21:1260–1268

Implications for Practice: Because of the increasing use of biologicals in oncology, many patients are at risk of developing antidrug antibodies (ADAs) during therapy. Although clinical consequences are uncertain, ADAs may affect pharmacokinetics, patient safety, and treatment efficacy. ADA detection and reporting is currently highly inconsistent, which makes it difficult to evaluate the clinical consequences. Standardized reporting of ADA investigations in the context of the aforementioned parameters is critical to understanding the relevance of ADA formation for each drug. Furthermore, the development of trials that specifically aim to investigate clinical prevention strategies in oncology is needed.

Introduction

Drug-induced immunogenicity has been recognized as a major challenge in the development of biological drugs. These biological drugs, such as proteins, peptides, and antibodies, consist of large and complex structures, and some of these structures may not belong to the patients' self-repertoire. Drug administration to patients may induce humoral immune responses, causing the formation of antidrug antibodies (ADAs). ADAs may inactivate the drug and cause a loss of targeting and/or an increased clearance of ADA-drug complexes, which may lead to suboptimal exposure and loss of efficacy [1, 2]. Patients who develop ADAs are also at risk for increased toxicity caused by the immune response that accompanies ADA formation, loss of drug targeting, or formation of highly immunogenic complexes [3–5].

Extensive research is being conducted to study the immunogenicity of biological drugs, such as anti-tumor necrosis factor α (anti-TNF-α) and factor VIII. This research is an important contribution to the current knowledge of risk factors for the immunogenicity, formation, and detection of ADAs and possible strategies to prevent ADA formation. It has become clear that immunogenicity is not solely dependent on the biological drug. Emerging data indicate that the development

Correspondence: Jan H.M. Schellens, M.D., Ph.D., Department of Clinical Pharmacology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Telephone: 31 (0)20 512 2446; E-Mail: j.schellens@nki.nl Received January 15, 2016; accepted for publication June 9, 2016; published Online First on July 20, 2016. 1083-7159/2016/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2016-0061

CME

of an immune response may be influenced by a variety of factors, such as dose, administration regimen, administration route, product quality and handling, comedication, patients' immune status, and genetic factors such as major histocompatibility complex genotype [2, 6]. As a result, formation of ADAs is subject to a high interindividual variability.

Although different medical fields have shown that ADA formation may have important consequences for therapy [5], little attention has been paid to ADA formation during anticancer therapy. Importantly, the risks and consequences of ADAs in oncology may not be identical to those in other fields (e.g., rheumatology and hematology). There are several factors that need to be specifically considered in oncology, such as the use of immunostimulatory compounds, the substantial number of immunocompromised patients, concomitant treatment, and immunosuppressing therapies.

This paper reviews the current knowledge on ADA formation in oncology, with the purpose of raising awareness and allowing a better understanding of the potential effects of ADAs. Topics that will be discussed include the incidence and clinical consequences of ADAs, the analytical methods that are used for detection, and the challenges in interpreting these data. Finally, in the last section of this review, we discuss challenges and potential strategies to deal with ADA formation in clinical practice, such as changes in the treatment regimen and concomitant treatment with immunosuppressive drugs.

Incidence of ADAs in Oncology

The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) published guidelines to recommend evaluation of immunogenicity of therapeutic proteins at the earliest stage of drug development and every subsequent stage [4, 7]. Clinical evaluation is of high importance, because currently no tools are available to adequately predict clinical immunogenicity based on (pre)clinical data. To study the reported immunogenicity of biological anticancer agents in clinical development, a focused PubMed literature review was performed, including the keywords "oncology" OR "cancer" AND "immunogenicity OR antidrug-antibodies" AND "clinical trial" NOT vaccine (a full description of methods is provided in the supplemental online Appendix). Among the 81 reviewed studies with biological anticancer agents, ADAs were detected in 63%. This number indicates that the majority of compounds in oncology are immunogenic and induce ADA formation. Recently, the intrinsic immunogenicity of monoclonal antibodies (mAbs) has been reduced by the transition from murine to chimeric, humanized, and fully human mAbs [8]. Our data support this as well for the mAbs used in oncology. The incidence of ADA formation was significantly less for human agents compared with humanized ($p = .03$), chimeric ($p = .007$), and murine ($p = .004$) agents (Fig. 1). However, even for human mAbs, ADAs are detected for 26.3%.

Eight studies reported the presence of pre-existing ADAs before the start of treatment [9–15]. Although the incidence of ADAs after treatment was not significantly different between trials with and without pre-existing ADAs (75% vs. 62%, $p = .70$) patients with pre-existing ADAs may develop ADAs faster and in higher quantities [12]. However, these ADAs can also be transient, and postdose ADA status can become negative [10, 16].

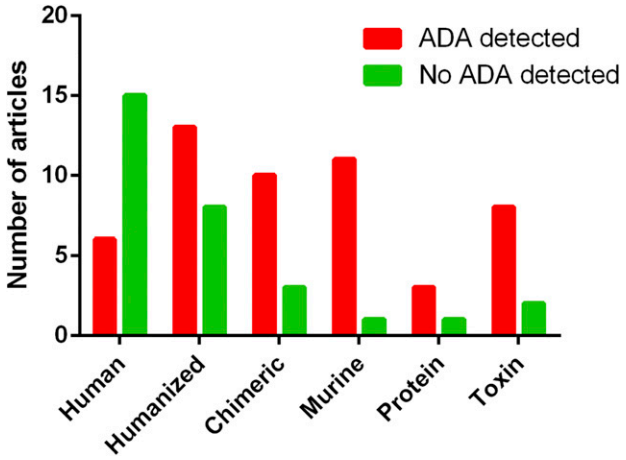

Figure 1. Detection of ADAs for murine, chimeric, humanized, human monoclonal antibodies, protein drugs, and toxins.
Abbreviation: ADA, antidrug antibody.

Clinical Relevance

In order to understand the clinical consequences of ADA formation, it is necessary to determine the impact on pharmacokinetics (PK), efficacy, and toxicity. For the majority of agents, the clinical relevance of ADA formation is not well established. In clinical trial reports, the titers and percentages of ADA-positive patients are often summarized, but the consequences of ADAs are not investigated. In the following sections, we discuss the relation between ADAs and these clinical parameters.

Consequences of Antidrug Antibody Formation on Pharmacokinetics, Efficacy, and Toxicity

Pharmacokinetics

ADAs can alter the PK profile of biologicals by causing accelerated clearance of ADA-drug complexes. This can lead to a lower and even subtherapeutic exposure (area under the curve [AUC]), as well as lower maximum concentrations (C_{max}) and a shorter elimination half-life ($t_{1/2}$), which have important consequences for treatment efficacy [9, 14, 17–22]. The impact of ADAs on PK is dependent on the affinity, the type of ADAs, and the amount of free drug that is not bound to ADAs. To understand the relevance, comparing maximum concentration levels (C_{max}) and exposure (AUC) in both the presence and absence of ADAs is essential. In the reviewed trials, data on ADAs are not routinely reported in context with PK. Among the 51 trials in which ADAs were detected, effects on PK were not explored in 67%, and 9 trials (18%) reported no influence of ADA formation on PK (Fig. 2). Only eight trials (16%) confirmed that PK was affected by ADAs. One of these, Posey et al., compared PK for cycles 1 and 4, knowing that 50% of the patients had ADA titers [17]. All but two patients showed similar C_{max} values for both cycles. One of these patients showed a very high ADA titer (460 ng/mL) and a 28% decrease in C_{max}. The other patient, who received a higher dose, showed a much lower ADA titer (86 ng/mL), but, surprisingly, showed an undetectable C_{max} during cycle 4. Possibly, more high-affinity ADAs were present in this patient. This illustrates that the relationship between ADA and PK is difficult to describe and is dependent on ADA titers and affinity. Reduced drug levels or

CME

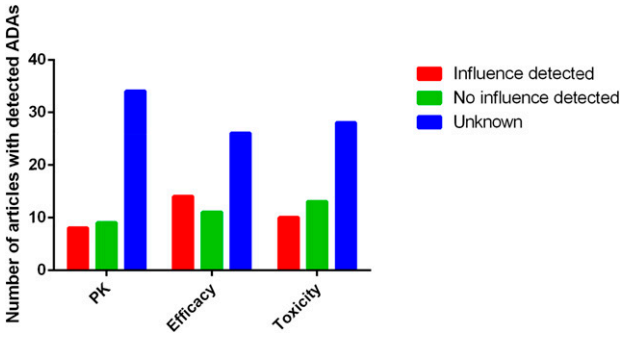

Figure 2. Influence of ADA formation on pharmacokinetics, efficacy, and toxicity.

Abbreviations: ADA, antidrug antibody; PK, pharmacokinetics.

exposures may indeed be direct results of ADA-drug binding, but they may also be a consequence of increased clearance or an increase in target-mediated drug disposition. In clinical development, the use of a PK-pharmacodynamic model can provide information on the relative contribution of ADAs [23].

The impact of ADAs on PK is dependent on the affinity, the type of ADAs, and the amount of free drug that is not bound to ADAs. To understand the relevance, comparing maximum concentration levels (C_{max}) and exposure (AUC) in both the presence and absence of ADAs is essential.

Efficacy

Even though ADAs can alter PK, this does not always translate to impaired therapeutic activity. Patients are specifically at risk of reduced efficacy if high titers of high-affinity neutralizing ADAs are present during treatment. Neutralizing ADAs bind to the variable regions of the antibody to prevent targeting, thus hampering the therapeutic activity [20]. In contrast, binding ADAs that bind to nonselective epitopes of the antibody, such as the Fc region, do not necessarily cause decreased therapeutic activity. However, both types of ADAs may lead to rapid clearance. In Yu et al., neutralizing ADAs against the chimeric mAb ch14.19 were formed, which prevented binding of ch14.19 to its target disialoganglioside (GD2) [24]. Three of eight patients in the study showed high ADA titers, yet these patients still had partial responses. Despite high titers, these ADAs may have had low affinities, or the neutralizing ADAs were formed after treatment was completed. In our dataset, out of 51 trials that detected ADA formation, 14 articles (27%) associated this with pharmacodynamic alterations or reduced efficacy, whereas in the majority of trials (51%), the effects were not explored (Fig. 2). Eleven trials (21%) found that ADAs had no effect on efficacy.

Toxicity

The most common toxic effects of ADAs are infusion-related reactions (IRRs) [25]. Multiple mechanisms can underlie an IRR. Hypersensitivity reactions are IgE-mediated [26], but IRRs can also be mediated by IgG or IgM ADAs. In hypersensitivity reactions, high titers of IgE ADAs are formed after drug exposure and bind to the FcεRI on mast cells. Upon re-exposure, a drug that binds to cell-bound IgE triggers degranulation of histamine, which causes an allergic reaction. As a consequence, treatment may be aborted to prevent severe allergic reactions upon retreatment [27]. In IgG-mediated reactions, binding of IgG to the drug may activate antibody-dependent cell-mediated toxicity. The Fc region of IgG ADAs binds to natural killer cells, causing a release of proinflammatory cytokines [28]. Furthermore, IgG aggregates and IgM are also capable of causing an inflammatory response through activation of the complement system [29]. Clinical manifestations of IRRs occur during or shortly after infusion of the drug and include a broad range of symptoms, including fever, skin rash, hypotension, gastrointestinal symptoms, and more. Because clinical symptoms are similar for each mechanism, it is difficult to distinguish between different types of IRRs. However, IRRs may also be independent of ADA formation and vice versa [27]. An example of a non-ADA-dependent IRR is cytokine release syndrome, in which cytokine-producing T cells cause a systemic inflammatory response [26].

In the majority of studies in our dataset, the relationship between ADAs and toxicity was not investigated. For 20% of the studies, ADAs were related to IRRs, such as rigors, coughing, dyspnea, back pain, rash, chills, chest tightness, hypotension, urticaria, bone pain, and fever (Fig. 2). Besides inducing immune-mediated reactions, ADAs can also indirectly affect toxicity by causing a loss of targeting. If ADAs neutralize the therapeutic agent and prevent binding of the drug to its target, drug-induced toxicity may be decreased [30]. We hypothesize that for immunotoxins and bispecific (e.g., T-cell activating) antibodies, the effect of neutralization by ADAs may be complicated: these antibodies consist of a targeting moiety and a pharmacologically active moiety. If the ADAs neutralize the targeting moiety, the drug may cause systemic toxicity because of loss of targeting.

Clinical Relevance of ADA Formation for Marketed Drugs

Among drugs investigated in the 81 reviewed trials, 9 are currently marketed. To assess the relevance of ADAs for the agents used in clinical practice more thoroughly, we reviewed 26 EMA and FDA drug reports [31–56]. Registered drugs have overcome many obstacles to be approved, including the hurdle of immunogenicity. For most registered biological anticancer drugs, only a low percentage of patients form ADAs, and these ADAs often do not have a clinical effect. This is true for commonly used drugs such as cetuximab (3.4%), trastuzumab (8%), rituximab (1%–2%), and panitumumab (3.8%). Remarkably, for bevacizumab, ramucirumab, trastuzumab emtansine, elotuzumab, and blinatumomab, the clinical consequences of ADAs are unknown, despite relevant percentages of ADA-positive patients (Table 1). The immune checkpoint inhibitors, such as nivolumab, pembrolizumab, and ipilimumab, have low immunogenicity (10%, 0.4%, and $<$2%, respectively), and ADAs are thought to have little impact on efficacy. Interestingly, the percentage of patients forming ADAs against nivolumab was higher when treatment was in combination with ipilimumab (21.9% vs. 10% in monotherapy) [57].

For ipilimumab (monotherapy), an ADA incidence of $<$2% was reported. However, the assay was sensitive to drug interference, leading to a potential underestimation of the number of ADA-positive patients [58]. Additional subset analyses indeed confirmed that the percentage of ADA-positive patients may approach 7% instead. This demonstrates

CME

Table 1. Overview of ADA relevance in registered biological anticancer agents based on European Public Assessment Reports unless otherwise indicated

Type	Drug	Target	Immunostimulatory effect	ADAs detected	Frequency (%)	Effects on PK	Effects on toxicity	Effects on efficacy
H	Panitumumab	EGFR	N	Yes	3.8	No	No	No
H	Ipilimumab	CTLA4	S	Yes	<2	ND	ND	No
H	Nivolumab	PD-1	S	Yes	10	No	No	No
H	Ofatumumab	CD20	I	No	0	NA	NA	NA
H	Necitumumab	EGFR	N	Yes	4.1 (FDA)	ND	No	ND
H	Daratumumab	CD38	I	No	0 (FDA)	NA	NA	NA
HZ	Obinutuzumab	CD20	I	Yes	6	ND	No	No
HZ	Bevacizumab	VEGF	N	Yes	0.63 (FDA)	ND	ND	ND
HZ	Trastuzumab	HER2	N	Yes	8	No	No	No
HZ	Ramucirumab	VEGFR2	N	Yes	2.2	ND	ND	ND
HZ	Pertuzumab	HER2	N	Yes	3	ND	Yes	ND
HZ	Pembrolizumab	PD-1	S	Yes	0.4	No	No	No
HZ	Elotuzumab	SLAMF7	S	Yes	18.5 (FDA)	ND	ND	ND
C	Rituximab	CD20	I	Yes	1 (i.v.) 2 (s.c.)	No	No	No
C	Siltuximab	IL-6	I	Yes	0.2	ND	No	No
C	Dinutuximab	GD2	N	Yes	17	Yes	No	ND
C	Cetuximab	EGFR	N	Yes	3.4	No	No	No
M	Ibritumomab	CD20	I	Yes	1.3 (FDA)	ND	No	ND
M	Catumaxomab	EpCAM + CD3	S	Yes	94	ND	No	ND
M	Tositumomab	CD20	I	Yes	80 (FDA)	ND	Yes	ND
T	Brentuximab vedotin	CD30	I	Yes	35	No	Yes	No
T	Trastuzumab emtansine	HER2	N	Yes	5.3	ND	ND	ND
P	IFN-α	IFN-α-R	S	Yes	2.9	ND	No	No
P/H	Aflibercept	VEGF	N	Yes	3.8	No	No	No
P	Aldesleukin	IL-2-R	S	Yes	70.8 (FDA)	Yes	ND	ND
H	Blinatumomab	CD19, CD3	S	Yes	1.4	ND	ND	ND

Abbreviations: C, chimeric; CTLA4, cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell-adhesion molecule; FDA, Food and Drug Administration; GD2, disialoganglioside; H, human; HER2, human epidermal growth receptor 2; HZ, humanized; I, inhibits immune system; IFN-α, interferon α; IL-6, interleukin 6; N, neutral to immune system; NA, not applicable; ND, no data; P, protein; PD-1, programmed death 1; S, stimulates immune system; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.
Source: [31–56].

the importance of knowing the strengths and weaknesses of the assay to interpret the results correctly.

Tositumomab, catumaxomab, brentuximab-vedotin, and aldesleukin are registered drugs that are highly immunogenic. These drugs either consist of a toxin conjugate, are a recombinant form of human protein, or are murine mAbs, and they induce ADAs in 35% (brentuximab-vedotin) to 94% (catumaxomab) of patients. ADAs during tositumomab and brentuximab-vedotin therapies increase toxicity, whereas for aldesleukin, only PK is affected. In all these cases, the relation to efficacy was not investigated. For catumaxomab, no clinical consequences were described in the drug report. Phase I data suggest that ADAs were formed mostly after the last infusion of catumaxomab, making it unlikely that these ADAs are clinically relevant [59].

Assessment of Immunogenicity

The clinical relevance can only be assessed when reliable and valid data on ADA formation are collected for the drug of interest. Whereas drug detection assays are relatively easy to develop and interpret because the detection target is clear, this is more difficult for ADA assays because the ADA population is heterogeneous. Furthermore, it is unclear which ADAs are clinically relevant, and detection is complicated by interference of the drug and ADA-drug complexes. In our dataset, the most popular method for ADA detection is enzyme-linked immunosorbent assay (ELISA), including direct [60], sandwich [61], bridging [62], and competitive ELISAs [16]. Other methods include high-performance liquid chromatography [63], electrochemiluminescence (ECL) assays [10, 64–66], radiometric assays [17, 67], radioimmunoassays [63, 68–70], and cytotoxicity assays [71, 72] (Fig. 3). The results are qualitative reports of the patient's ADA status (positive/negative), often accompanied by titer levels.

For a proper understanding of assay results, it is essential to know which type of ADA is detected by the assay. ADAs may consist of multiple immunoglobulin subclasses and are either

CME

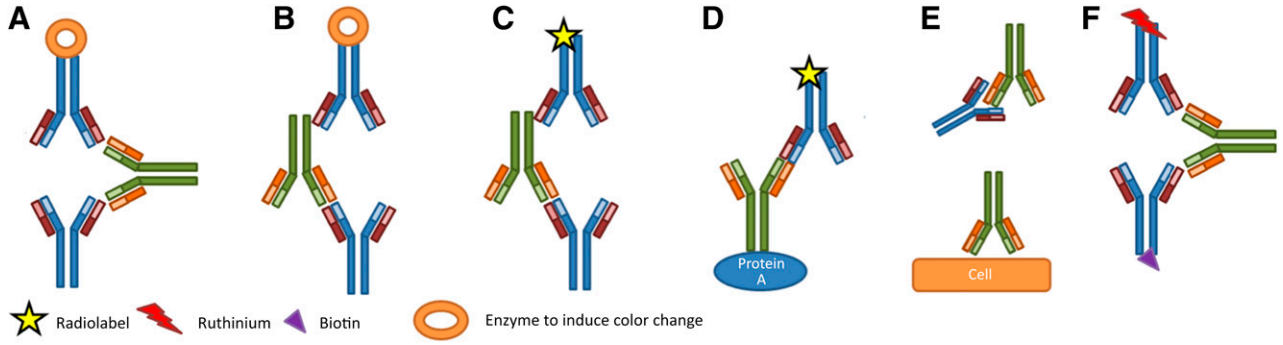

Figure 3. Schematic representation of techniques used to detect antidrug antibodies (ADAs). **(A):** Bridging enzyme-linked immunosorbent assay (ELISA) with drug as binding agent and enzyme-linked drug as idiotype-detecting agent. **(B):** Sandwich ELISA with drug as binding agent and enzyme-linked secondary antibody as isotype-detecting agent. **(C):** Radioimmunoassay with radiolabeled drug binding to ADAs. **(D):** Antigen-binding test in which IgG from serum is pulled down by protein A bound to a solid carrier, and radiolabeled drug is added and binds to ADAs. **(E):** Cytotoxicity assays measure ADA-induced alterations in cytotoxic effects of the drug. **(F):** Bridging electrochemiluminescence assays measure electrochemical signals from the ruthinium-labeled drug bound to the ADA-biotin-streptavidin complex.

freely circulating or drug-bound. However, most assays, including ELISAs, measure only free IgG subclasses. Drug-bound ADAs and important immunoglobulin subclasses, such as IgE, are not detected, which may lead to an underestimation of the incidence and the titer of ADAs [73].

To manage drug interference, samples can be acidified to separate drug-ADA complexes [74]. Samples can also be taken before dosing, when drug concentrations are low [74]. Another option is using the antigen-binding test (ABT). ABTs are less vulnerable to drug interference and can measure moderate amounts of ADA-drug immunocomplexes [5]. In this assay, ADAs of the IgG class, including those that are drug-bound, are pulled down during the first step of the assay using protein A. Then, radiolabeled drug binds to the ADA, and the radiation signal is measured (Fig. 3). If the samples are acidified before the ABTs, the assay is even more tolerant to drug interference [5]. However, in spite of their increased resistance to drug interference, even ABTs may give an underestimation, because not all immunoglobulin subtypes are measured.

Different assays detect different subclasses and idiotypes of ADAs, and currently no assay is able to detect all ADAs. This is one of the reasons why ADA formation across different trials cannot be accurately compared. To increase sensitivity, a tiered approach can be applied, consisting of a screening assay, a confirmatory assay, and, finally, characterization of the ADAs [75]. In a number of trials, ADAs were already detected before treatment, and these samples were occasionally deemed false-positive [15]. By using the aforementioned tiered approach, these samples should be analyzed for ADA with a confirmatory assay to truly validate that these patients are ADA-negative. An example of this approach is the phase I trial of AGS-1C4D4, a human anti-prostate stem cell antigen monoclonal antibody [76]. An ECL test served as the screening test in which three patients tested ADA-positive. A second assay was performed for confirmation, which yielded negative results. Therefore, the patients were considered negative for the presence of anti-AGS-1C4D4 antibodies.

Although accurately detecting the presence and incidence of ADAs is important, it may be even more crucial to characterize the effects of the detected ADAs. Assays that determine the presence of neutralizing antibodies, such as cytotoxicity assays [72], can select for those ADAs that affect efficacy.

To summarize, ADA assays should be rationally designed to detect the most relevant range of ADAs, and results should be consistently reported to allow an understanding of the characteristics and consequences of the detected ADAs. Furthermore, standardization of assays is essential to allow comparison of results on ADA formation between different trials. For this, the recently developed guidelines for ADA assays for clinical use published by the ABIRISK consortium could be used [75].

Prevention Strategies

Although reducing intrinsic immunogenicity of the drug is a successful approach to reduce ADA formation, clinical results show that this is not sufficient to prevent ADA formation in all patients. Several prevention strategies have been applied in clinical practice, and their potential will be explored in this section.

Tolerance Induction by Adaptations to the Treatment Regimen

Several studies indicate that immunogenicity can be reduced by increasing the exposure through high-dose and high-frequency therapy [5, 27, 77–80]. The effects of high-dose and high-frequency treatment were first observed in hemophilia patients treated with factor VIII after the doses were increased from normal treatment regimen to twice daily infusions [80]. In patients treated with infliximab, the incidence of ADA formation was 28% after a single dose of infliximab compared with 6% after repeated doses [27, 81]. It is hypothesized that the tolerance is mediated by activation of regulatory T cells [82] and apoptosis of effector T cells [83]. However, it is unknown whether this is a consequence of increased plasma concentrations (C_{max} and C_{ss}), prolonged exposure ($t_{1/2}$), higher exposure (AUC), or any combination of these.

In oncology, the effects of modifications to the treatment regimen are conflicting. Among the nine studies that reported ADA formation for different doses, the majority found that ADA

CME

formation was not dose-dependent [21, 71, 84–86], and only two studies confirmed a decrease in ADA formation with higher doses [17, 19].

The main limitations of high-dose or high-frequency treatment are the therapeutic and toxic effects of the drug. One possible method to avoid these is by administering only the immunogenic part of the molecule without the pharmacologically active moiety, as was done by Somerfield et al. [78]. In this study, patients treated with alemtuzumab received the nonbinding SM3 shortly before treatment. SM3 differs from alemtuzumab in only a single point mutation, which prevented binding to CD52. In this way, high doses may be administered without causing unacceptable toxicity. This strategy reduced the percentage of ADA-positive patients significantly from 74% to 21%. However, introducing this additional compound into the clinic may be very costly and time-consuming, and occupation of the target by this compound may be a problem.

In contrast to the results of high-dose and high-frequency treatment, four studies reported that tolerance was induced by decreasing the exposure through lower doses, continuous infusion, or subcutaneous administration [71, 87–89]. For the humanized antibody trastuzumab, ADA formation was twice as high after intravenous administration (14.6%) as after subcutaneous administration (7.1%) in equivalent doses [89]. For the antimesothelin immunotoxin SS1P, a bolus injection administered in 3 days every other day induced ADAs in 88% of patients, whereas an equivalent dose of a 10-day continuous infusion induced ADAs in 75% [72].

In summary, it is clear that adaptations to the dose and treatment regimen can alter immunogenicity. Most evidence is available for tolerance induction by high-dose and high-frequency therapy, but this does not appear to be effective for all drugs. Modifications to the treatment regimen are relatively easy adjustments and should be considered based on successful cases that have been described in the literature.

Immunosuppression

In rheumatology, the use of immunosuppressive agents is an effective treatment strategy that simultaneously reduces the frequency of ADA formation up to 46% [90–94]. Concomitant treatment with methotrexate (MTX) in low (5–10 mg), intermediate (12.5–20 mg), or high (>22.5 mg) weekly doses successfully led to reduction of ADA formation in adalimumab-treated rheumatoid arthritis patients in a dose-dependent manner [90]. A similar effect was observed in rheumatoid arthritis patients who received infliximab. After a single dose of infliximab, ADAs were formed in 53%, 21%, and 7% (1, 3, and 10 mg of infliximab per kg, respectively) of the patients. When combined with 7.5 mg of MTX weekly, the incidence was, respectively, 15%, 7%, and 0% of patients [92]. Azathioprine, 6-mercaptopurine, hydrocortisone, and rituximab have also been applied in rheumatology, but results have been inconclusive [94–97].

In oncology, immunosuppression can be effective for the treatment of hematological malignancies, but for many solid tumors, immunosuppression may be undesired. Among the articles we reviewed, only two investigated the effects of immunosuppression and showed that cyclophosphamide and cyclosporin could not prevent ADA formation [98, 99].

Unique challenges regarding the use of immunosuppression to prevent ADA formation in oncology may be the large group of immunocompromised patients and the increasing use of immunostimulatory agents such as immunotoxins, interleukin-2, CD3, CD19, and CD28 agonists, anti-programmed death 1, and anti-cytotoxic T-lymphocyte antigen 4. Both factors may alter the risk of ADA formation (decrease and increase, respectively), and for these patients special prevention strategies may be required. Our data showed no significant difference ($p = 1.0$) in ADA formation between the trials with immunostimulatory agents (75% detected ADAs [$n = 20$]), immunosuppressing agents (69% [$n = 13$]), and nonimmunotherapies (56% [$n = 48$]) (Fig. 4). No data were available to compare ADA formation between immunocompromised and immunocompetent patients. Although some trials investigated immunostimulatory agents combined with immunosuppression, effects on treatment efficacy and ADA formation could not be determined based on the reported data [18]. However, it is clear that, despite immunosuppression, patients are still at risk of ADA formation [23, 100]. This is illustrated by the trial by Welt et al. [30] with the humanized antibody huA33, in which concomitantly administered chemotherapy led to bone marrow suppression in 10 of 16 patients. The majority of ADA-negative patients were immunocompromised (4 of 6), but one patient with severe neutropenia showed high and increasing ADA titers.

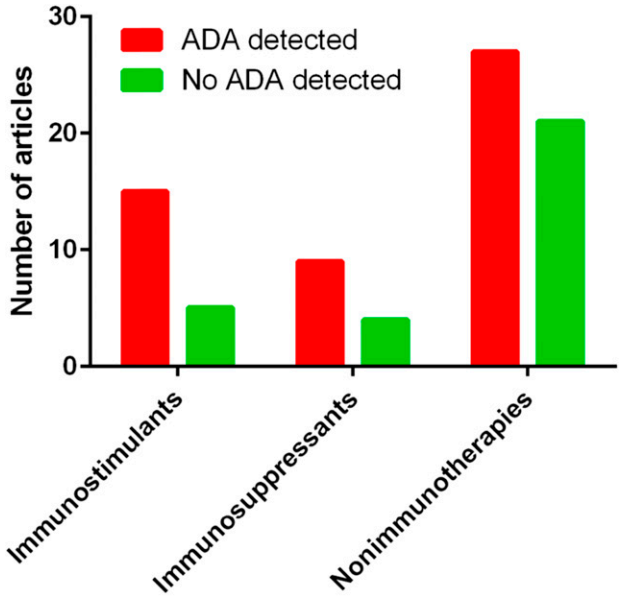

Figure 4. Detection of ADAs for immunostimulants, immunosuppressants, and nonimmunotherapies.
Abbreviation: ADA, antidrug antibody.

Although some trials investigated immunostimulatory agents combined with immunosuppression, effects on treatment efficacy and ADA formation could not be determined based on the reported data. However, it is clear that, despite immunosuppression, patients are still at risk of ADA formation.

A feasible prevention strategy for oncology may be targeted B-cell inhibition with anti-CD20 agents, such as rituximab, veltuzumab, or obinutuzumab, which inhibit de novo humoral antibody responses. Several trials have been

CME

done with B-cell-inhibiting agents, but these did not detect effects on ADA formation [61, 69, 72, 87, 101, 102]. Hassan et al. showed that rituximab was able to induce full depletion of CD20-positive B cells, but this did not prevent ADAs targeted toward the therapeutic drug [103]. Maeda et al. [104] described a case of a rituximab-treated mantle-cell lymphoma patient, who developed high titers of antirituximab antibodies leading to a decreased exposure, and Sausville et al. [69] detected ADAs in 75% of B-cell lymphoma patients treated with the B-cell-targeting anti-CD22 immunotoxin IgG-RFB4-SMPT-dgA.

These trials show that ADA formation is still possible despite B-cell depletion, but it is not clear if the frequencies, titers or onset may be reduced. Taken together, immunosuppression has successfully reduced ADA formation in rheumatology but evidence for immunosuppression in oncological patients, and in combination with immunotherapies or immunocompromisation is lacking. The absence of observed effects of immunosuppression on ADAs may be explained by the fact that these clinical trials were not designed to investigate this thoroughly. Clinical trials specifically designed to determine the effect of immunosuppressive therapy, such as anti-CD20, on antidrug antibody formation may determine whether immunosuppression is useful in oncology.

Conclusion

We confirmed that the majority of biological anticancer agents in clinical development induce ADA formation. For most agents that were EMA or FDA approved, ADAs have been detected but have not been an obstacle for approval. However, even among marketed agents, important gaps in the data on ADA formation exist. In most cases the consequences of ADAs for efficacy, pharmacokinetics and toxicity are not thoroughly investigated. Routine investigation of the relationship between ADAs and these parameters may help to establish the clinical relevance and explain variability in drug responses and safety.

Furthermore, inconsistent reporting and heterogeneity in detection methods complicate interpretation of the obtained results regarding ADA formation. Consistent reporting of the method of assessment, the incidence and characteristics of the detected ADAs will allow proper interpretation and comparison of the relevance of ADA formation. We would like to encourage the use of standardized terms for immunogenicity reporting as published by the ABIRISK consortium [75].

If ADAs are considered clinically relevant for a specific agent, strategies for prevention or management of the consequences may be designed. One potential method that is quick and easy to investigate is regimen adjustment. Although the mechanisms are not yet fully understood, clinically relevant effects have been observed, as we described in this review. More aggressive measures to be considered include immunosuppressive treatment with for example anti-CD20 or methotrexate, although more research is necessary to evaluate whether these methods are feasible in oncology.

Author Contributions

Conception/Design: Emilie M.J. van Brummelen, Willeke Ros, Jan H.M. Schellens
Collection and/or assembly of data: Emilie M.J. van Brummelen, Willeke Ros
Data analysis and interpretation: Emilie M.J. van Brummelen, Willeke Ros, Gertjan Wolbink, Jos H. Beijnen, Jan H.M. Schellens
Manuscript writing: Emilie M.J. van Brummelen, Willeke Ros
Final approval of manuscript: Emilie M.J. van Brummelen, Willeke Ros, Gertjan Wolbink, Jos H. Beijnen, Jan H.M. Schellens

Disclosures

Gertjan Wolbink: Pfizer (RF), UCB, Mundipharma, Abbvie, Bristol-Myers Squibb, Pfizer (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. van Schie KA, Hart MH, de Groot ER et al. The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region. Ann Rheum Dis 2015;74:311–314.

2. van Schouwenburg PA, van de Stadt LA, de Jong RN et al. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. Ann Rheum Dis 2013;72:104–109.

3. Hansel TT, Kropshofer H, Singer T et al. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010;9:325–338.

4. U.S. Food and Drug Administration. Guidance for industry: Adaptive design clinical trials for drugs and biologics. 2010.

5. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol 2013;9:164–172.

6. Deehan M, Garcês S, Kramer D et al. Managing unwanted immunogenicity of biologicals. Autoimmun Rev 2015;14:569–574.

7. European Medicines Agency. Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins . 2007.

8. Hwang WYK, Foote J. Immunogenicity of engineered antibodies. Methods 2005;36:3–10.

9. Colnot DR, Quak JJ, Roos JC et al. Phase I therapy study of 186Re-labeled chimeric monoclonal antibody U36 in patients with squamous cell carcinoma of the head and neck. J Nucl Med 2000;41:1999–2010.

10. Murakami H, Ikeda M, Okusaka T et al. A phase I study of MEDI-575, a PDGFRα monoclonal antibody, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2015;76:631–639.

11. Hartmann F, Renner C, Jung W et al. Anti-CD16/CD30 bispecific antibodies as possible treatment for refractory Hodgkin's disease. Leuk Lymphoma 1998;31:385–392.

12. Papadopoulos KP, Isaacs R, Bilic S et al. Unexpected hepatotoxicity in a phase I study of TAS266, a novel tetravalent agonistic Nanobody® targeting the DR5 receptor. Cancer Chemother Pharmacol 2015;75:887–895.

13. Pietzner K, Vergote I, Santoro A et al. Rechallenge with catumaxomab in patients with malignant ascites: Results from the SECIMAS study. Med Oncol 2014;31:308.

14. MacDonald GC, Rasamoelisolo M, Entwistle J et al. A phase I clinical study of intratumorally administered VB4-845, an anti-epithelial cell adhesion molecule recombinant fusion protein, in patients with squamous cell carcinoma of the head and neck. Med Oncol 2009;26:257–264.

15. Becerra CR, Conkling P, Vogelzang N et al. A phase I dose-escalation study of MEDI-575, a PDGFRα monoclonal antibody, in adults with advanced solid tumors. Cancer Chemother Pharmacol 2014;74:917–925.

16. Plummer R, Attard G, Pacey S et al. Phase 1 and pharmacokinetic study of lexatumumab in patients with advanced cancers. Clin Cancer Res 2007;13:6187–6194.

17. Posey JA, Ng TC, Yang B et al. A phase I study of anti-kinase insert domain-containing receptor antibody, IMC-1C11, in patients with liver metastases from colorectal carcinoma. Clin Cancer Res 2003;9:1323–1332.

18. Posey JA, Khazaeli MB, Bookman MA et al. A phase I trial of the single-chain immunotoxin SGN-10 (BR96 sFv-PE40) in patients with advanced solid tumors. Clin Cancer Res 2002;8:3092–3099.

CME

19. Scott AM, Wiseman G, Welt S et al. A phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res 2003;9: 1639–1647.

20. Caron PC, Schwartz MA, Co MS et al. Murine and humanized constructs of monoclonal antibody M195 (anti-CD33) for the therapy of acute myelogenous leukemia. Cancer 1994;73(suppl): 1049–1056.

21. Hank JA, Gan J, Ryu H et al. Immunogenicity of the hu14.18-IL2 immunocytokine molecule in adults with melanoma and children with neuroblastoma. Clin Cancer Res 2009;15:5923–5930.

22. MacDonald GC, Rasamoelisolo M, Entwistle J et al. A phase I clinical study of VB4-845: Weekly intratumoral administration of an anti-EpCAM recombinant fusion protein in patients with squamous cell carcinoma of the head and neck. Drug Des Devel Ther 2009;2:105–114.

23. Gómez-Mantilla JD, Trocóniz IF, Parra-Guillén Z et al. Review on modeling anti-antibody responses to monoclonal antibodies. J Pharmacokinet Pharmacodyn 2014;41:523–536.

24. Yu AL, Uttenreuther-Fischer MM, Huang CS et al. Phase I trial of a human-mouse chimeric anti-disialoganglioside monoclonal antibody ch14.18 in patients with refractory neuroblastoma and osteosarcoma. J Clin Oncol 1998;16:2169–2180.

25. Baert F, Noman M, Vermeire S et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348: 601–608.

26. Vultaggio A, Nencini F, Pratesi S et al. Manifestations of antidrug antibodies response: Hypersensitivity and infusion reactions. J Interferon Cytokine Res 2014;34:946–952.

27. Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity, and associated infusion reactions. Mt Sinai J Med 2005;72:250–256.

28. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: From structure to effector functions. Front Immunol 2014;5:520.

29. Karsten CM, Köhl J. The immunoglobulin, IgG Fc receptor and complement triangle in autoimmune diseases. Immunobiology 2012;217:1067–1079.

30. Welt S, Ritter G, Williams C Jr. et al. Preliminary report of a phase I study of combination chemotherapy and humanized A33 antibody immunotherapy in patients with advanced colorectal cancer. Clin Cancer Res 2003;9:1347–1353.

31. European Medicines Agency. European public assessment report for Vectibix (panitumumab). 2015.

32. European Medicines Agency. European public assessment report for Opdivo (nivolumab). 2016.

33. European Medicines Agency. European public assessment report for Arzerra (ofatumumab). 2016.

34. European Medicines Agency. European public assessment report for Keytruda (pembrolizumab). 2016.

35. European Medicines Agency. European public assessment report for MabThera (rituximab). 2016.

36. European Medicines Agency. European public assessment report for Sylvant (siltuximab). 2015.

37. European Medicines Agency. European public assessment report for Unituxin (dinutuximab). 2015.

38. European Medicines Agency. European public assessment report for Erbitux (cetuximab). 2015.

39. European Medicines Agency. European public assessment report for Removab (catumaxomab). 2014.

40. European Medicines Agency. European public assessment report for Adcetris (brentuximab vedotin). 2016.

41. European Medicines Agency. European public assessment report for Kadcyla (trastuzumab emtansine). 2016.

42. European Medicines Agency. European public assessment report for IntronA (interferon alfa-2b). 2016.

43. European Medicines Agency. European public assessment report for Zaltrap (aflibercept). 2015.

44. European Medicines Agency. European public assessment report for Blincyto (blinatumomab). 2015.

45. U.S. Food and Drug Administration. Potrazza (necitumumab) prescribing information. 2015.

46. U.S. Food and Drug Administration. Darzalex (daratumumab) prescribing information. 2015.

47. U.S. Food and Drug Administration. Avastin (bevacizumab) prescribing information. 2011.

48. U.S. Food and Drug Administration. Empliciti (elotuzumab) prescribing information. 2015.

49. U.S. Food and Drug Administration. Zevalin (ibritumomab) prescribing information. 2008.

50. U.S. Food and Drug Administration. Bexxar (Tositumomab; Iodine 131 tositumomab) approval label. 2003.

51. U.S. Food and Drug Administration. Proleukin (aldesleukin) approval label. 2012.

52. European Medicines Agency. European public assessment report for Herceptin (trastuzumab). 2016.

53. European Medicines Agency. European public assessment report for Gazyvaro (obinutuzumab). 2015.

54. European Medicines Agency. European public assessment report for Yervoy (ipilimumab). 2016.

55. European Medicines Agency. European public assessment report for Cyramza (ramucirumab). 2016.

56. European Medicines Agency. European public assessment report for Perjeta (pertuzumab). 2016.

57. U.S. Food and Drug Administration. Opdivo (nivolumab) prescribing information. 2015.

58. U.S. Food and Drug Administration. Yervoy (ipilimumab) prescribing information. 2013.

59. Ruf P, Kluge M, Jäger M et al. Pharmacokinetics, immunogenicity and bioactivity of the therapeutic antibody catumaxomab intraperitoneally administered to cancer patients. Br J Clin Pharmacol 2010;69:617–625.

60. Wakelee HA, Patnaik A, Sikic BI et al. Phase I and pharmacokinetic study of lexatumumab (HGS-ETR2) given every 2 weeks in patients with advanced solid tumors. Ann Oncol 2010;21:376–381.

61. Scheinberg DA, Straus DJ, Yeh SD et al. A phase I toxicity, pharmacology, and dosimetry trial of monoclonal antibody OKB7 in patients with non-Hodgkin's lymphoma: Effects of tumor burden and antigen expression. J Clin Oncol 1990;8:792–803.

62. Morris MJ, Eisenberger MA, Pili R et al. A phase I/IIA study of AGS-PSCA for castration-resistant prostate cancer. Ann Oncol 2012;23:2714–2719.

63. Wong JYC, Chu DZ, Yamauchi DM et al. A phase I radioimmunotherapy trial evaluating 90yttrium-labeled anti-carcinoembryonic antigen (CEA) chimeric T84.66 in patients with metastatic CEA-producing malignancies. Clin Cancer Res 2000;6:3855–3863.

64. Rasche L, Duell J, Castro IC et al. GRP78-directed immunotherapy in relapsed or refractory multiple myeloma—results from a phase 1 trial with the monoclonal immunoglobulin M antibody PAT-SM6. Haematologica 2015;100:377–384.

65. von Pawel J, Harvey JH, Spigel DR et al. Phase II trial of mapatumumab, a fully human agonist monoclonal antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 1 (TRAIL-R1), in combination with paclitaxel and carboplatin in patients with advanced non-small-cell lung cancer. Clin Lung Cancer 2014;15:188–196.e2.

66. Salgia R, Patel P, Bothos J et al. Phase I dose-escalation study of onartuzumab as a single agent and in combination with bevacizumab in patients with advanced solid malignancies. Clin Cancer Res 2014;20:1666–1675.

67. Forero A, Meredith RF, Khazaeli MB et al. Phase I study of 90Y-CC49 monoclonal antibody therapy in patients with advanced non-small cell lung cancer: effect of chelating agents and paclitaxel co-administration. Cancer Biother Radiopharm 2005; 20:467–478.

68. Chiorean EG, Hurwitz HI, Cohen RB et al. Phase I study of every 2- or 3-week dosing of ramucirumab, a human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2 in patients with advanced solid tumors. Ann Oncol 2015;26:1230–1237.

69. Sausville EA, Headlee D, Stetler-Stevenson M et al. Continuous infusion of the anti-CD22 immunotoxin IgG-RFB4-SMPT-dgA in patients with B-cell lymphoma: A phase I study. Blood 1995;85: 3457–3465.

70. Caron PC, Jurcic JG, Scott AM et al. A phase 1B trial of humanized monoclonal antibody M195 (anti-CD33) in myeloid leukemia: Specific targeting without immunogenicity. Blood 1994; 83:1760–1768.

71. Kreitman RJ, Hassan R, Fitzgerald DJ et al. Phase I trial of continuous infusion anti-mesothelin recombinant immunotoxin SS1P. Clin Cancer Res 2009;15:5274–5279.

72. Kreitman RJ, Tallman MS, Robak T et al. Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. J Clin Oncol 2012;30:1822–1828.

73. Hart MH, de Vrieze H, Wouters D et al. Differential effect of drug interference in immunogenicity assays. J Immunol Methods 2011;372: 196–203.

74. Mikulskis A, Yeung D, Subramanyam M et al. Solution ELISA as a platform of choice for development of robust, drug tolerant immunogenicity assays in support of drug development. J Immunol Methods 2011;365:38–49.

75. Rup B, Pallardy M, Sikkema D et al. Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: Recommendations of the Innovative Medicines Initiative ABIRISK consortium. Clin Exp Immunol 2015;181:385–400.

76. Antonarakis ES, Carducci MA, Eisenberger MA et al. Phase I rapid dose-escalation study of AGS-1C4D4, a human anti-PSCA (prostate stem cell antigen) monoclonal antibody, in patients with castration-resistant prostate cancer: A PCCTC trial. Cancer Chemother Pharmacol 2012;69:763–771.

CME

77. Michallet M-C, Saltel F, Flacher M et al. Cathepsin-dependent apoptosis triggered by supra-optimal activation of T lymphocytes: A possible mechanism of high dose tolerance. J Immunol 2004; 172:5405–5414.

78. Somerfield J, Hill-Cawthorne GA, Lin A et al. A novel strategy to reduce the immunogenicity of biological therapies. J Immunol 2010;185:763–768.

79. Brackmann HH, Gormsen J. Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder. Lancet 1977;2:933.

80. Brackmann HH, Oldenburg J, Schwaab R. Immune tolerance for the treatment of factor VIII inhibitors–twenty years' 'Bonn protocol'. Vox Sang 1996;70(suppl 1):30–35.

81. Rutgeerts P, Feagan BG, Lichtenstein GR et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–413.

82. De Groot AS, Moise L, McMurry JA et al. Activation of natural regulatory T cells by IgG Fc-derived peptide "Tregitopes". Blood 2008;112: 3303–3311.

83. Michallet M-C, Saltel F, Flacher M et al. Cathepsin-dependent apoptosis triggered by supra-optimal activation of T lymphocytes: A possible mechanism of high dose tolerance. J Immunol 2004; 172:5405–5414.

84. Tolcher AW, Sweeney CJ, Papadopoulos K et al. Phase I and pharmacokinetic study of CT-322 (BMS-844203), a targeted Adnectin inhibitor of VEGFR-2 based on a domain of human fibronectin. Clin Cancer Res 2011;17:363–371.

85. Crombet T, Torres O, Neninger E et al. Phase I clinical evaluation of a neutralizing monoclonal antibody against epidermal growth factor receptor. Cancer Biother Radiopharm 2001;16:93–102.

86. Manzke O, Tesch H, Borchmann P et al. Locoregional treatment of low-grade B-cell lymphoma with CD3xCD19 bispecific antibodies and CD28 costimulation. I. Clinical phase I evaluation. Int J Cancer 2001;91:508–515.

87. Forero A, Weiden PL, Vose JM et al. Phase 1 trial of a novel anti-CD20 fusion protein in pretargeted radioimmunotherapy for B-cell non-Hodgkin lymphoma. Blood 2004;104:227–236.

88. Martinsson-Niskanen T, Riisbro R, Larsson L et al. Monoclonal antibody TB-403: A first-in-human, phase I, double-blind, dose escalation study directed against placental growth factor in healthy male subjects. Clin Ther 2011;33:1142–1149.

89. Jackisch C, Kim S-B, Semiglazov V et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: Updated results from the phase III HannaH study. Ann Oncol 2015;26:320–325.

90. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis 2012;71: 1914–1915.

91. Maini R, St Clair EW, Breedveld F et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. Lancet 1999;354:1932–1939.

92. Maini RN, Breedveld FC, Kalden JR et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–1563.

93. Garman RD, Munroe K, Richards SM. Methotrexate reduces antibody responses to recombinant human alpha-galactosidase A therapy in a mouse model of Fabry disease. Clin Exp Immunol 2004;137: 496–502.

94. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947–1955.

95. Farrell RJ, Alsahli M, Jeen YT et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: A randomized controlled trial. Gastroenterology 2003;124: 917–924.

96. Vande Casteele N, Gils A, Singh S et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol 2013; 108:962–971.

97. Messinger YH, Mendelsohn NJ, Rhead W et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genet Med 2012;14:135–142.

98. Oratz R, Speyer JL, Wernz JC et al. Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (XMMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: Results of a phase II trial. J Biol Response Mod 1990;9: 345–354.

99. Selvaggi K, Saria EA, Schwartz R et al. Phase I/II study of murine monoclonal antibody-ricin A chain (XOMAZYME-Mel) immunoconjugate plus cyclosporine A in patients with metastatic melanoma. J Immunother Emphasis Tumor Immunol 1993;13: 201–207.

100. Harding FA, Stickler MM, Razo J et al. The immunogenicity of humanized and fully human antibodies: Residual immunogenicity resides in the CDR regions. MAbs 2010;2:256–265.

101. Witzig TE, Tomblyn MB, Misleh JG et al. Anti-CD22 90Y-epratuzumab tetraxetan combined with anti-CD20 veltuzumab: A phase I study in patients with relapsed/refractory, aggressive non-Hodgkin lymphoma. Haematologica 2014;99:1738–1745.

102. Morschhauser F, Leonard JP, Fayad L et al. Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: Phase I/II results. J Clin Oncol 2009;27:3346–3353.

103. Hassan R, Williams-Gould J, Watson T et al. Pretreatment with rituximab does not inhibit the human immune response against the immunogenic protein LMB-1. Clin Cancer Res 2004;10:16–18.

104. Maeda T, Yamada Y, Tawara M et al. Successful treatment with a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) for a patient with relapsed mantle cell lymphoma who developed a human anti-chimeric antibody. Int J Hematol 2001; 74:70–75.

See http://www.TheOncologist.com for supplemental material available online.

This article is available for continuing medical education credit at CME.TheOncologist.com.