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## Clinical implications of immunogenicity

Bartelds, G.M.

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## Chapter 1

# General introduction

### **Biological therapeutics**

Biologicals include a wide range of medicinal products created by biological instead of chemical processes. Biologicals can consist of sugars, proteins, nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. They are isolated from a variety of natural sources — human, animal, or microorganism — or are produced by biotechnology methods and other technologies. Gene-based and cellular biologicals often are at the forefront of biomedical research, and may be used to treat a wide scope of medical conditions for which no other or only suboptimal treatments are available. (1) In most cases, the term "biologicals" is used for a class of medications that are produced by processes involving recombinant DNA technology. Usually the term "biologicals" is further restricted to recombinant therapeutic proteins that influence disease processes by blocking specific signal peptides. Treatment with biological therapeutics has been approved for many conditions such as cancer, cardiovascular disease, inflammatory diseases, macular degeneration, transplant rejection, multiple sclerosis and viral infections. These biological therapeutics can vary from substances that are nearly identical to the body's own signalling proteins to monoclonal antibodies to receptor constructs.

### **Impact of biological therapeutics**

Biological therapeutics had and have a major impact on many medical fields, such as rheumatology, oncology, cardiology, dermatology, gastroenterology, neurology, and others. In most of these disciplines, biologicals have added major therapeutic advances to the treatment of many diseases, including some for which no effective therapies were available, and others where previously existing therapies were inadequate.

### **TNF inhibitors in rheumatology**

In the field of rheumatology, the introduction of biological therapeutics that inhibit Tumor Necrosis Factor (TNF) has greatly improved treatment. TNF is a pro-inflammatory cytokine of which increased synovial expression levels were demonstrated during inflammatory disease. (2) Biologicals that block TNF and inhibit the binding of this cytokine to its receptor on effector cells interrupt the inflammatory process perpetuated by TNF. (3) Presently there are five TNF inhibitors available: infliximab, adalimumab, etanercept, golimumab and certolizumab pegol. Infliximab is a chimeric (mouse-human) monoclonal antibody (mAb), adalimumab and golimumab are fully human mAbs, etanercept is a TNF receptor Fc-fusion protein, and certolizumab is a Fab antibody fragment which is linked to polyethylene glycol (PEG). TNF inhibitors are widely used and have shown beneficial results in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). (4-6)

### **Anti-TNF treatment of rheumatoid arthritis**

Rheumatoid arthritis is a systemic inflammatory disease characterized mainly by inflammation of joints. Approximately 1% of the population is affected. (7) The disease is characterized by a chronic synovitis which can result in destruction of cartilage and bone, which may lead to joint damage, functional disability, loss of labour capacity, decreased quality of life and shortened life expectancy. (8) TNF inhibitors have been approved for clinical use for a decade and have changed dramatically the landscape of therapeutics used for rheumatoid arthritis. All TNF inhibitors have been shown to decrease disease activity and substantially retard or abrogate radiographic deterioration in rheumatoid arthritis. (9-13)

### **Non-response to TNF-inhibitors**

Despite the advantages of biological therapeutics, there are downsides as well. The majority of rheumatoid arthritis patients respond well to treatment with TNF inhibitors, however, a substantial proportion, 30 to 40%, still has persistent disease activity or flare of disease activity despite treatment with TNF blocking therapy. (10;12;14;15) Reasons for this lack of clinical response are still subject of investigation.

### **Adverse events**

In addition, biological therapeutics have been associated with adverse events, such as reactivation of latent tuberculosis, other granulomatous infections and soft tissue and joint infections. (16-19) Furthermore, there have been concerns for lymphoma, solid tumours, non-melanoma skin cancers, possible exacerbation of congestive heart failure, multiple sclerosis, and new onset psoriasis. (20-23)

### **Pharmacoeconomic aspects**

Furthermore, the expanding use of biological therapeutics has led to pharmacoeconomic concerns, because the costs for biologic therapies have been dramatically higher than for conventional (pharmacological) medications. This factor is particularly relevant since many biological medications are used for the treatment of chronic diseases, such as rheumatoid arthritis or inflammatory bowel disease, or for otherwise untreatable cancer during the remainder of life. The cost of treatment with a typical monoclonal antibody therapy for relatively common indications is generally in the range of € 7,000-14,000 per patient per year. In the Netherlands yearly costs for treatment of rheumatoid arthritis with TNF inhibitors vary per TNF inhibitor from approximately € 9,000 to € 15,000. (24)

### **Immunogenicity of biological therapeutics**

All biologicals can induce an unwanted immune response. (25) The immunogenicity of biological therapeutics is the ability to provoke an immune response. The immune response against native biologicals differs from the immune response against designed biologicals containing new foreign epitopes. An immune response against native human hormones, growth factors and cytokines occurs only when the natural tolerance against these biologicals is broken. The frequency of this type of immunogenicity is low. Immunogenicity against designed biologicals reflects more the normal immune response against a foreign intruder. (26) This immune response in the form of anti-drug antibodies is associated with diminished serum drug levels and a diminished treatment response in several conditions and for several biologicals. (9;27-31) Furthermore the development of anti-drug antibodies has been associated with potentially severe adverse events such as infusion reactions with anti-infliximab and aplastic anemia caused by anti-epoetin. (30;32) The information provided on immunogenicity in the first large clinical trials on infliximab and adalimumab for the treatment of RA was limited. Measurement techniques were described very briefly and the reported low incidence of anti-drug antibodies and their lack of clinical relevance does not correspond with data that were published more recently. In table 1 the data published on immunogenicity for the most important randomized clinical trials of adalimumab are summarized.

RCT Ref	Journal	Pub year	Disease	Pt no	Follow-up	Immunogenicity investigated	Assay	Sampling	
								Timepoints	Trough
(10)	Arthritis Rheum	2003	RA	271	24 wk	yes	double-capture ELISA	week 0, 4, 12, 24	ND
(52)	J Rheum	2003	RA	636	24 wk	no	NA	NA	NA
(38)	Ann Rheum Dis	2003	RA	284	12 wk	yes	double antigen ELISA	every 2 wks?	ND
(53)	Arthritis Rheum	2004	RA	619	52 wk	yes	double-capture ELISA	week 0, 24, 52	ND
(54)	Arthritis Rheum	2005	PsA	315	24 wk	no	NA	NA	NA
(45)	Gastroenterology	2006	CD	299	4 wk	yes	ND	ND	ND
(55)	Arthritis Rheum	2006	AS	208	24 wk	no	NA	NA	NA
(56)	J Am Acad Derm	2006	PsO	147	60 wk	no	NA	NA	NA
(57)	Arthritis Rheum	2006	RA	799	104 wk	no	NA	NA	NA
(58)	Gastroenterology	2007	CD	854	56 wk	no	NA	NA	NA
(43)	Gut	2007	CD	276	56 wk	yes	ND	every 4 to 8 weeks	ND
(47)	NEJM	2008	JIA	171	104 wk	yes	ND	ND	ND

RCT Ref	Incidence of anti-drug antibodies	Clinical response	Association with clinical response
(10)	3 of 271 AAA+ of whom 1 in placebo group	2 AAA+ pt (incl placebo) no ACR20 response	no
(52)	NA	NA	NA
(38)	4 of 284 AAA+	ND	no
(53)	4 (of 619?) AAA + of whom 1 in placebo group	ND	no
(54)	NA	NA	NA
(45)	2 patients AAA+ of whom 1 in the placebo group	ND	No
(55)	NA	NA	NA
(56)	NA	NA	NA
(57)	NA	NA	NA
(58)	NA	NA	NA
(43)	7 of 269 AAA+ (2.6%)	43% AAA+ remission wk 24, 29% remission wk 56	no
(47)	27 of 171 AAA+ (16%)	no association with discontinuation	no

**Table 1.** Overview of reporting on immunogenicity in large randomized clinical trials with adalimumab.

NA: not applicable; ND: not described; AAA: anti-adalimumab antibodies; wk: week; ELISA: Enzyme Linked Immunosorbent Assay. RA: Rheumatoid arthritis; PsA: Psoriatic arthritis; CD: Crohn's disease; AS: ankylosing spondylitis; PsO: Psoriasis; JIA: juvenile idiopathic arthritis.

### **Incidence of anti-drug antibodies**

The incidence of anti-drug antibodies varies widely between reported studies. This is dependent on the therapeutic itself and other factors like study population, dosing scheme, use of concomitant medication and the assays used to measure anti-drug antibodies. In general, in RA patients treated with infliximab 8%-52% of patients developed antibodies to infliximab (ATI) (9;14;27;33-35), in adalimumab treated patients 4,9%-44% (34;36-39) developed anti-adalimumab antibodies (AAA); in Crohn's disease 14%-75% developed ATI (30;40-42) and 2,6%-17% developed AAA (31;43-45); in juvenile idiopathic arthritis 37% developed ATI (46) and 17% AAA (47); in ankylosing spondylitis 29% (48) and 31% (49) of patients developed ATI and AAA, respectively; in psoriatic arthritis 18% of patients developed AAA (28) and in psoriasis patients 33.3% developed ATI (50) and 45% AAA. (51)

### **Consensus in the field of immunogenicity**

Consensus regarding the assessment of anti-drug antibodies is mandatory for a valid comparison of the immunogenicity of different drugs. The European Crohn's and Colitis Organisation (ECCO) launched a workshop to achieve understanding and consensus on important aspects of treatment with TNF inhibitors. (59) Points of concern have been recognized such as the extent of non-response and possible preventive measurements, pharmacokinetics of TNF inhibitors and the importance thereof for the response rates, and how treatment can be optimized. In addition, one of the ECCO goals is to assess the clinical relevance of immunogenicity and to gain insight into the clearance of biological drugs whether or not in complex with anti-drug antibodies. Furthermore, an important formulated aspect is the standardization of the measurement of anti-drug antibodies and serum drug levels. (59)

### **This thesis**

Hence the immunogenicity of therapeutic antibodies is an emerging important new field of research and many issues regarding immunogenicity have to be elucidated. As described before, publications on the subject were limited and in the large clinical trials on monoclonal antibodies in rheumatology the formation and impact of anti-drug antibodies were only briefly described. Since then, the number of publications on immunogenicity has grown extensively. The goal of this thesis is to provide knowledge on immunogenicity of therapeutic monoclonal antibodies (mAbs) and to show the implications relevant for clinical practice: how do clinicians have to deal with immunogenicity in their clinical practice? (26)

The first part of this thesis focuses on the effect of anti-drug antibody development on clinical response to treatment. Then, two chapters are dedicated to describing how determining immunogenic response against mAbs could assist in clinical decision making, especially focusing on subsequent treatment after failure to a first TNF inhibitor. Patient and treatment related factors that influence anti-drug antibody formation are discussed in the next section. In addition to clinical outcome, adverse events associated with anti-drug antibody development are described. In the final chapter, the evidence gained by these studies are put in perspective and clinical implications and future directions are discussed.

In **Chapter 2** a case report is described of a patient with rheumatoid arthritis who developed high levels of anti-drug antibodies against the fully human monoclonal antibody adalimumab. The association with undetectable serum drug levels and disease activity during treatment is reported.

**Chapter 3** investigates the immunogenicity of adalimumab in a cohort of 121 consecutive patients with rheumatoid arthritis treated with adalimumab during 28 weeks follow-up. The incidence of anti-

adalimumab antibody formation and the effect on clinical efficacy is discussed as well as the association with low serum drug levels and the importance of concomitant methotrexate use.

**Chapter 4** describes the course of anti-drug antibody formation in a population of 272 rheumatoid arthritis patients during long-term (3 year) follow up. This chapter shows how the development of anti-drug antibodies jeopardizes the long-term efficacy of adalimumab treatment in clinical practice.

**Chapter 5** postulates the hypothesis that assessing the antibody response against a first monoclonal antibody could help in estimating the response to a second monoclonal antibody. Data from clinical practice are shown to support this hypothesis.

In **Chapter 6** a proof of concept study is described to provide further evidence for the hypothesis raised in the previous chapter. Chapter 6 shows how determining anti-drug antibodies in a non-responding patient can be part of a personalized treatment regimen, because it can be helpful in deciding in which patient switching to another TNF-inhibitor could be beneficial and meaningful.

**Chapter 7** describes how patient-related genetic factors could be associated with the development of anti-drug antibodies. The association between antibodies against adalimumab and IL-10 single nucleotide polymorphisms is discussed.

**Chapter 8** elaborates on the association between patient-related genetic factors and the possible association with the formation of anti-drug antibodies. This chapter focuses on the association between the IgG allotypic phenotype of patients and the frequency of anti-drug antibodies.

In addition to genetic factors, concomitant immunosuppressing treatment, e.g. concomitant methotrexate, appears to be associated with the development of anti-drug antibodies. **Chapter 9** is a review on the effect of the immunosuppressants methotrexate and azathioprine on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies. Evidence coming from a wide variety of medical conditions is taken into account.

**Chapter 10** shows that the development of anti-drug antibodies may lead to serious adverse events. The continuous formation of immune complexes, if treatment is continued despite the presence of anti-drug antibodies, may be not so harmless as currently perceived.

In **Chapter 11** the most important findings described in this thesis are summarized and put into perspective in view of the current developments in the field of biological drug treatment. Implications for clinical practice and directions for future research are given.

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