Chapter 9
Fetal and Neonatal Illnesses Caused or Influenced by Maternal Transplacental IgG and/or Therapeutic Antibodies Applied During Pregnancy

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Contents

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Abstract The human fetus is protected by the mother's antibodies. At the end of the pregnancy, the concentration of maternal antibodies is higher in the cord blood, than in the maternal circulation. Simultaneously, the immune system of the fetus begins to work and from the second trimester, fetal IgM is produced by the fetal immune system specific to microorganisms and antigens passing the maternal-fetal barrier. The same time the fetal immune system has to cope and develop tolerance and T_{REG} cells to the maternal microchimeric cells, latent virus-carrier maternal cells and microorganisms transported through the maternal-fetal barrier.

The maternal phenotypic inheritance may hide risks for the newborn, too. Antibody mediated enhancement results in dengue shock syndrome in the first 8 month of age of the baby.

A series of pathologic maternal antibodies may elicit neonatal illnesses upon birth usually recovering during the first months of the life of the offspring. Certain antibodies, however, may impair the fetal or neonatal tissues or organs resulting prolonged recovery or initiating prolonged pathological processes of the children.

The importance of maternal anti-idiotypic antibodies are believed to prime the fetal immune system with epitopes of etiologic agents infected the mother during her whole life before pregnancy and delivery.

The chemotherapeutical and biological substances used for the therapy of the mother will be transcytosed into the fetal body during the last two trimesters of pregnancy. The long series of the therapeutic monoclonal antibodies and conjugates has not been tested systematically yet. The available data are summarised in this chapter.

The innate immunity plays an important role in fetal defence. The concentration of interferon is relative high in the placenta. This is probably one reason, why the therapeutic interferon treatment of the mother does not impair the fetal development.

9.1 Introduction

At term, the amount of maternal IgG antibody is higher in the neonate than in the mother. This pattern holds when the IgG antibody is an anti-TNFα medication. A specific Fc receptor neonate (FcRn) facilitates transfer of the IgG antibodies across the syncytiotrophoblast into the fetal circulation (Kane and Acquah 2009). Due to the high rate of IgG transfer near term, babies have been found to have similar blood levels of infliximab to the mother. By discontinuing this drug 8–10 weeks prior to delivery, the baby will likely be born with no or minimal

serum levels, thus avoiding immunosuppression in a young infant. Though there are some suggestive data that certolizumab does not cross the placenta as easily as the IgG derived drugs due to the pegylation of the molecules (Clowse 2010).

In early human placenta the exchange tissue area (villi) is formed around the entire surface of the conceptus. This placental shape is called diffuse placenta. By the third month of pregnancy, only the villi near the initial site of implantation have persisted, leading to the formation of the disc-shaped placenta. Although chorioallantoic placenta in humans begins functioning already by the end of the fourth week of pregnancy, this process is completed with the formation of disk-shaped placenta (Sadler 2004). During the first trimester, the human fetus is surrounded by two fluid cavities, i.e., the inner amniotic cavity and the outer extra-embryonic coelomic cavity.

The chorioallantoic placenta is only formed of fetal vessels' endothelium and trophoblastic layer, bathed directly in the maternal blood (Van der Aa et al. 1998). For 8 out of 15 **monoclonal therapeutic compounds**, for which toxicity studies (in a broad sense) were performed, no significant maternal, fetal, or neonatal toxicity was observed. For the remaining seven products, the most common adverse effects on reproduction and development were reduced fetal weight, increased abortion rates, and reduction in fertility, indicating the general toxicity of these compounds (Pentsuk and van der Laan 2009). Twenty-four (59%) of the 41 children had one or more congenital anomalies that are part of VACTERL association, but only one child (with maternal etanercept administration) was diagnosed with VACTERL association i.e. V: vertebral defects, A: anal atresia or imperforate anus, C: cardiac abnormalities [atrial septal defect, ventricular septal defect, and tetralogy of Fallot], T: tracheoesophageal fistula or tracheal atresia/stenosis, E: esophageal atresia, R: radial and or renal abnormalities, and pre-axial L: limb abnormalities (Carter et al. 2006, 2009).

9.2 Neonatal Antibody-Dependent Enhancement of Immune Response

Fc-FcγR interactions play a critical role in the biological function of antibody and are likely to be instrumental in preventing or modulating lentiviral infections. Antibody responses that depend on Fc-FcγR interactions may help widen the spectrum and increase the potency of vaccine-induced antibodies (Forthal and Moog 2009). Maternofetal transmission of non-neutralising dengue virus specific antibodies result in the development of hemorrhagic fever of the newborns even in the case of the first infection with a heterotypic virus. The mechanism is the formation of non-neutralised neonatal virus and heterotypic maternal IgG complexes, which will be taken up by endothelial and hematopoetic cells by (virus-AbFc)-FcγR pinocytosis. The risk disappears after the 8th month of age of the children, when the maternal IgG disappeared from the circulation of the children (Libraty et al. 2009). This phenomenon has been observed in the case of other **Flaviviruses and enteroviruses**, too (Ferenczi et al. 2008; Wang et al. 2010b).

Dengue serotype cross-reactive cytotoxic lymphocytes (CTL) clones showing high avidity for antigen produce higher levels of inflammatory cytokines than serotype-specific clones. High avidity cross-reactive memory CTL may produce inflammatory cytokines during the course of secondary infection, contributing to the pathogenesis of vascular leak. These cells appear to be subsequently deleted leaving a more serotype-specific memory CTL pool. Antibody-dependent **enhancement ADE is neither a sufficient nor an absolutely necessary precondition for the development of severe shock syndrome or hemorrhagic disease.** CTL response to a viral infection can be modulated by the infection history of an individual in a manner likely to contribute to disease severity (Dong et al. 2007; Lühn et al. 2007).

Respiratory syncytial virus (RSV) enhancer activity of transplacental maternal antibodies have been observed first by Osiowy et al. (1994). RSV infection is also enhanced by non-neutralising antibodies (Johnson and Graham 2004). Vaccination using inactivated virus particles were caused immune enhancement in the case of RSV in contrast to other, for example influenza viruses (Openshaw et al. 2001; Ye et al. 2004). Cytotoxic T-cells, cytokines and interferon induction by Toll-like receptors may potentiate this enhancement (Mobbs et al. 2002; Boukhvalova et al. 2006; Tregoning et al. 2008; Lee et al. 2008a, b; Nguyen et al. 2010; Ubol and Halstead 2010). Tumour necrosis factor β1 block of cell-replication enhances RSV-replication (Gibbs et al. 2009). The evidence of the enhancer effect of non-neutralizing antibodies to RSV can be prevented by the treatment of children at increased risk with neutralizing monoclonal antibodies directed against the fusion (F) protein of RSV (Motavizumab and/or Palivizumab). This monoclonal antibodies were not found to cause harmful effects in connection with the preventive treatment of neonates and infants at risk (Martin-Mateos 2007; Nieri et al. 2009; Weisman 2009; Groothuis et al. 2011). Anti-RSV-F protein specific antibodies can prevent also the RSV-*S. pneumoniae* enhancement of respiratory infections (Hament et al. 2005).

The blocking of influenza specific anti-neuraminidase antibodies using **anti-idiotypes** indirectly enhanced the hemagglutination-inhibition titers of antisera (Dowdle et al. 1972). Influenza H1 specific antisera were found to enhance virus replication in a macrophage-like cell line P388D1, when P388D1 cells, previously had been treated with neuraminidase to remove the viral receptors (Ochiai et al. 1990).

9.3 Neonatal Illnesses Caused by Pathological Maternal Antibodies

9.3.1 Systemic Lupus Erythemadosus (SLE)

Systemic lupus erythemadosus (SLE), is characterised by antibodies towards dsDNA and Ro52 (E3 ligase regulating TLR signalling) which, are present several years before the onset of disease and the neonatal disease is caused by some of these transplacental antibodies (Watson et al. 1984). Systemic lupus erythematosus (SLE)

is the most common autoimmune disease affecting women of reproductive age and is associated with poor maternal and fetal outcomes. CD4(+)CD25(+) T_{REG} cells are a subset of T lymphocytes with potent immunosuppressive activity that play crucial roles in controlling immunological self tolerance. Evidence suggests that they are augmented in pregnancy, especially in the first trimester, suggesting an important role in early placental development. The literature describing T_{REG} cells in SLE is conflicting, but SLE is associated with reduced numbers and functionally defective T_{REG} cells, which may predispose pregnant women with the disease to pregnancy complications. This article discusses the role of T_{REG} cells in SLE and pregnancy, and how these cells may contribute to poor pregnancy outcome in SLE-affected women (Blois et al. 2007; Clark et al. 2005).

SLE was induced by interferon α administration, and by a specific stimuli i.e. sunshine exposure and smoking. The HLA-DR3 haplotype was also found to be a risk factor (Klareskog et al. 2010). Alcohol consumption was shown to be protective in these illnesses. Vaccinations in adult age was found to be innocuous concerning the risk of RA according to the results of a case–control study when common vaccinations 5 years before onset of RA had been followed up. The effects of environment, however, are unknown for the **neonatal heart block** in p200 and Ro52 positive women, but the active immunisation does not increase the risk of it (Bengtsson et al. 2010a, b).

In SLE and Sjögren's disease pregnants with high antibody titers against the p200 epitope of Ro52 are those who almost exclusively carry the risk that their fetuses will develop neonatal heart block between gestational weeks 20–24. Monitoring during these period the anti-Ro52 antibodies, steroid treatment or preventive *in utero* pacemaker treatment may reduce the risk (Wahren-Herlenius 2010). Foetal genes, maternal age and infectious agents may contribute to the risk of congenital heart block. Especially inherited high level interferon production was also shown to be a risk factor for SLE (Niewold et al. 2007).

Heparin treatment and intravenous gamma globulin (IVIg) treatment and specific anti-idiotypes reduce the risk of the disease (Clark et al. 2010). IVIg enhanced the anti-Id antibody response in pregnant women with anti-La/SSB antibodies. The Id:anti-Id ratio was significantly higher in mothers whose offspring developed neonatal lupus compared to mothers who gave birth to a healthy child ($P < 0.0001$). Removal of anti-Id antibodies substantially increased the reactivity against La(349–364) in sera from five of seven mothers tested. IVIg from batches administered to mothers who gave birth to a healthy child had an Id:anti-Id activity ratio of <1, in contrast to that given to mothers who gave birth to a child with neonatal lupus (Brucato et al. 2010, 2011; Routsias et al. 2011).

The main pathomechanism of the development of neonatal lupus erythematosus is the transcytosis of maternal antibodies, and probably microchimeric cells. The pathogenesis of the maternal disease is extremely complex as summarised recently by Perl (2010) and Perl et al. (2010).

Mitochondrial hyperpolarization underlies mitochondrial dysfunction, depletion of ATP, oxidative stress, abnormal activation, and death signal processing in lupus T cells. Nitric oxide production, expression of endogenous retroviral and repetitive

elements such as HRES-1, (the long interspersed nuclear elements 1), Trex1, interferon alpha (IFN-alpha), toll-like receptors 7 and 9 (TLR-7/9), high-mobility group B1 protein, extracellular signal-regulated kinase, DNA methyl transferase 1, histone deacetylase, spleen tyrosine kinase, proteasome function, lysosome function, endosome recycling, actin cytoskeleton formation, the nuclear factor kappa B pathway, and activation of cytotoxic T cells were shown to be components of the pathogenesis (Varghese et al. 2011).

The HRES-1 human endogenous retrovirus (ERV) encodes a 28k nuclear autoantigen and a 24-kD small GTPase, termed HRES-1/Rab4. HRES-1/p28 is a target of cross-reactive antiviral antibodies, whereas HRES-1/Rab4 regulates the surface expression of CD4 via endosome recycling. HRES-1/Rab4 is overexpressed in lupus T cells where it correlates with increased recycling of CD4 and CD3 and contributes to downregulation of CD3/TCRs via lysosomal degradation. ERV proteins may trigger lupus through structural and functional molecular mimicry, whereas the accumulation of ERV-derived nucleic acids stimulates interferon and anti-DNA antibody production. ERV proteins may trigger lupus through structural and functional molecular mimicry, whereas the accumulation of ERV-derived nucleic acids stimulate interferon and anti-DNA antibody production in SLE (Perl 2010; Perl et al. 2010).

These complex of pathogenetic factors many of them influenced by pregnancy results the clinical disease of the newborns (Ruiz-Irastorza and Khamashta 2011).

Neonatal lupus erythematosus (NLE) is an inflammatory disorder of neonates characterized by transient cutaneous lesions and/or congenital heart block. The cutaneous lesions usually heal with minimal scarring within 5–10 months, but may be delayed for many months in occasional cases. The maternal antibodies disappear from the circulation of the newborns within 8–10 months, the long-lasting clinical symptoms indicate, that irreversible events, or impairment of fetal cells occur during the fetal life.

Photosensitivity is recognized as a component of this syndrome. U1-ribonucleoprotein (U1-RNP) specific antibodies can be detected in the circulation of the newborns. Skin and cardiac manifestations coexist in only 10% of patients. Hepatic, hematological and, less commonly, pulmonary, neurological and gastrointestinal abnormalities may also be present (Watson et al. 1984; Perez et al. 2011).

Neonatal lupus is a model of passively acquired autoimmunity in which a mother-, who may have systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS) or may be entirely asymptomatic-synthesizes antibodies to SSA/Ro and/or SSB/La ribonucleoproteins that enter the fetal circulation via trophoblast FcRn receptors and presumably cause tissue injury (Lee 1990) as mentioned above. Congenital heart block is a passively transferred autoimmune condition, which affects the children of mothers with Ro/SSA autoantibodies. During pregnancy, the antibodies are transported across the placenta and affect the fetus. It has been previously demonstrated that antibodies directed to the 200–239 amino acid (aa) stretch of the Ro52 component of the Ro/SSA antigen correlate with the development of congenital heart block. The antibody recognition is dependent on a partly alpha-helical fold within the putative leucine zipper of the 200–239 aa stretch (Ottosson et al. 2005).

Smith (Sm) antigen, which is highly specific for SLE is composed of at least nine different polypeptides with molecular weights ranging from 9 to 29.5 kDa, B (B1, 28 kDa), B′ (B2, 29 kDa), N (B3, 29.5 kDa), D1 (16 kDa), D2 (16.5 kDa), D3 (18 kDa), E (12 kDa), F (11 kDa), and G (9 kDa). SLE patients develop antibodies against the SM complexes of the small nuclear RNAs U1 to U6 in the mother and recently these were also detected in neonatal LE patient (Ortiz-Santamaria et al. 2010).

In neonatal lupus, mothers with high **anti-idiotypic antibody** activity against anti-La autoantibodies are at lower risk of giving birth to an unhealthy child, as compared with mothers without anti-idiotypic antibodies.

Usually anti-idiotypic antibodies may confer protection from the harmful effect of autoantibodies in certain autoimmune diseases (Tzioufas and Routsias 2010). IVIg enhanced the anti-Id antibody response in pregnant women with anti-La/SSB antibodies. A high Id:anti-Id ratio in both the IVIg preparation and the maternal serum may explain the absence of an effect of IVIg in preventing recurrent neonatal lupus in some cases (Routsias et al. 2011).

The children of the mothers suffering from SLE and Sjögren's syndromes are at risk also for other rheumatic/autoimmune diseases without carrying antibodies reactive with SSA/Ro or SSB/La antigens. Among the siblings without neonatal lupus developed later juvenile rheumatoid arthritis, Hashimoto thyroiditis, psoriasis and iritis, diabetes mellitus, congenital hypothyroidism and nephrotic syndrome (Martin et al. 2002; Winter and Schatz 2003).

Experimental systemic lupus erythemetosus could be induced in mice using immunisation with anti-idiotype antibodies (Ab2) specific to the anti-DNA-specific monoclonal antibodies (Mendlovic et al. 1989). Identical twins of mothers suffering from SLE had also transient neonatal bullous skin disease (Nakajima et al. 2011).

9.3.2 Rheumatoid Arthritis (RA)

Autoimmunity has been defined as a normal physiological state with control mechanisms that prevent autoimmunity from progressing to overt pathology. The onset of a subset of **rheumatoid arthritis (RA)** begins with appearance of citrullinated protein antigen (CPA) positivity when tolerance to certain citrullinated proteins/peptides is broken supported by certain HLA-DR haplotypes (HLA-DR04 and HLA-DRB1 in smokers). Local expression of peptidylarginine deiminases and occasional elevation of inflammatory cytokines can be measured (Klareskog et al. 2010). Methotrexate was significantly more effective than placebo in preventing progression to this disease state in anti-CPA-positive patients with **undifferentiated arthritis (UA)** whereas no difference between methotrexate and placebo was seen in the ACPA-negative group of patients with undifferentiated arthritis (UA; arthritis without arthralgia). The risk of RA was lower in this group without treatment (Ehrenstein et al. 2004; van Dongen et al. 2007). The treatments using therapies – infliximab (a tumour necrosis factor (TNF-α) blocker) and abatacept (T cell

costimulation inhibitor; anti-CD80 and anti-CD86) did not result in significant improvement of the ACPA patients with UA (Saleem et al. 2008; Emery et al. 2010). The analysis of **myeloid-related proteins** (MRP-8/MRP-14) in serum is an excellent tool for the diagnosis of systemic onset of **juvenile idiopathic arthritis (JIA)**, allowing early differentiation between patients with systemic-onset of JIA and those with other inflammatory diseases. MRP-8/MRP-14 and IL-1β represent a novel positive feedback mechanism activating phagocytes via two major signaling pathways of innate immunity (TLR4) during the pathogenesis of systemic-onset of JIA (Frosch et al. 2009). The rheumatoid arthritis was found to be improved during pregnancy probably due to galactosylation of IgG molecules (Förger and Østensen 2010).

Women with RA can acquire the **susceptibility allele through microchimeric cells**. Very high amounts (0.9% of total PBMCs) of DRB1*04 microchimerism in patients with RA were observed. Similarly, DRB1*01 microchimeric DNA was observed in significantly higher quantities in women with RA compared with healthy control subjects. In contrast, there was no difference between women with RA and control subjects when microchimerism for non–RA-associated alleles (HLA–DQB1*02 and DRB1*15/16) was analyzed (Rak et al. 2009). By analogy to graft-versus-host disease (GVHD), pioneer studies on microchimerism in women with scleroderma proposed direct and indirect recognition mechanisms as underlying reactions of microchimeric cells (Nelson 2002). In GVHD, donor cells invade the recipient, which is not what is observed with microchimerism in patients with RA. However, the presence of DRB1*01 microchimerism (0.03%) and DRB1*04 microchimerism (0.9%) is not negligible, with frequencies among total host PBMCs similar to the frequencies of antigen-specific CD4+ T cells, which thus are sufficient to impact the host immune reactions. The haplotypes of the patients influence the progression of the rheumatoid arthritis, too (Liu et al. 2007).

9.3.3 Epidermodysplasia Bullosa Aquisita

Autoimmune **neonatal bullous skin disease** caused by placental transfer of maternal IgG autoantibodies is rare. It has been reported in neonates born to mothers with pemphigus vulgaris, pemphigus foliaceus, and gestational pemphigoid. Vertically acquired congenital autoimmune blistering disorders appear to be self-limited and resolve with supportive therapy, concomitant with the presumed clearance of maternal autoantibodies from the neonate's circulation (Abrams et al. 2011).

9.3.4 Antiphospholipid Antibody Syndrome (APAS)

Antiphospholipid antibody syndrome (APAS) is regarded as the most frequently acquired risk factor for thrombophilia. Thrombophilia is the tendency to thrombosis. The antiphospholipid antibody syndrome (APAS) is a disorder of recurrent vascular thrombosis, pregnancy loss and thrombocytopenia, associated with persistently raised

levels of anti-phospholipid antibodies (APA). The APA are phospholipids (part of a cell's membrane) recognized by the body as foreign and antibodies are produced against them. Maternal autoimmune diseases significantly reduce the pregnancy outcome of the women. The most frequent illnesses were antiphospholipid syndrome, antiphospholipid syndrome associated with a rheumatic disease (APS/RD), other RD patients, isolated autoantibodies (autoAbs) in the absence of a definite autoimmune disease (aAbs) and reactive arthritis or spondyloarthropathies. Of these patients, 50.6% had previous pregnancy complications with an anamnestic live-birth rate of 43.4%. In these patients, 10.4% of pregnancies resulted in preterm delivery and 10.9% newborns had low weight at delivery. APS/RD patients had the worse outcome: 17.6% resulted in miscarriage, 14.3% resulted in growth restriction and 50% resulted in preterm delivery. This result was mainly due to patients with APS/systemic lupus erythematosus (SLE) that had the lowest gestational age at delivery (30.8 ± 3.56 weeks) and the lowest newborn weight (Canti et al.2011). Antiphospholipid syndrome was suggested to be the result of antibodies, directed against cardiolipin as a result of antigenic mimicry. The suspected antigen is beta-2-glycoprotein-I (B2GPI) (Sherer et al. 2007).

Clinically significant are lupus anticoagulant, anticardiolipin antibodies and anti-β 2 glycoprotein-I (anti-β2 GP-I) antibody. Neonates born to mothers with primary APS are at risk of prematurity, being small for gestational age, and having thrombocytopenia (Chou et al. 2009). Antiphospholipid antibodies (aPL) can impair the physiologic development of a fetus during pregnancy not only by causing thrombosis of the placental vessels, but also by directly binding throphoblast cells and modifying their functions (Tincani et al. 2009).

Transplacentally transferred antiphospholipid antibodies act as a risk factor, but are not usually a sufficient condition for thrombosis and other thrombophilic risk factors should be systematically evaluated. Long-term studies of children born to antiphospholipid-antibody-positive mothers provided the evidence of possible neurodevelopmental changes in these children and regular neuropsychological assessments are recommended. Antiphospholipid-antibody-related thromboses in children are frequently associated with multiple antiphospholipid antibody positivity and concomitant presence of inherited prothrombotic disorders can be also detected in addition to nonthrombotic manifestations, particularly hematological, skin and neurological manifestations (Avcin 2008). Treatment of pregnant women with APAS results in marked improvement in the live birth rate (4.6–85.7%). However, complications like preeclampsia and intrauterine growth restriction (IUGR) occur even after treatment, requiring strict monitoring and timely delivery. Aberrant concentrations of fetuin A and heat shock protein might have also role in the preeclamptic inflammation (Molvarec et al. 2009a, b; Dadhwal et al. 2011).

9.3.5 Thyrotrophin Receptor Stimulating Antibodies (TRAb)

Foetal/neonatal disease is due to transplacental **thyrotrophin receptor stimulating antibodies** (TRAb). It's extremely important recognising and treating Graves'

disease in mothers as soon as possible, because a thyrotoxic state may have adverse effects on the outcome of pregnancy and both on the foetus and newborn. **Neonatal Grave's disease** tends to resolve spontaneously within 3–12 weeks as maternal thyroid stimulating immunoglobulins are cleared from the circulation but subsequent development may be impaired by perceptual motor difficulties. Hashimoto's thyroiditis is a very common autoimmune thyroid disease. In presence of maternal Hashimoto's thyroiditis, there are usually no consequences on foetal thyroid, even if antiTPO and antiTg antibodies can be found in the newborn due to transplacental passage. However there are some reports describing foetal and neonatal hyperthyroidism in the affected mothers' offspring (Radetti et al. 2002; Hemminki et al. 2010). A number of autoimmune diseases; especially **autoimmune thyroid diseases**, **erythema nodosum** and **sarcoidosis** parity might somehow be involved in maternal disease development (Jørgensen et al. 2011). Maternal thyroid status assessment and treatment improves fetal outcomes and neuropsychological developmental of the newborn (Staii et al. 2010).

9.3.6 Juvenile Myasthenia Gravis

Juvenile myasthenia gravis is associated with antibodies to the acetylcholine receptor (AChR) in most patients. Thymoma is rare, but often malignant in children. The frequency of juvenile myasthenia gravis with antibodies to the musclespecific kinase (MuSK) varies markedly in different countries. Neonatal myasthenia gravis associated with MuSK antibodies is often a severe and protracted albeit transient disease (Béhin et al. 2008; Evoli 2010). Transient **neonatal myasthenia gravis (MG)** is a human model of passively transferring the disease. Although all newborn babies of myasthenic mothers have anti-AChR antibodies at birth (Morel et al. 1988; Tzartos et al. 1990), only a small percentage of them (10–15%) express the myasthenic syndrome (Namba et al. 1970). The myasthenic symptoms usually appear a few hours after birth and their average duration is about 3 weeks. Neonatal myasthenia gravis is transiently transferred from the mothers to the newborn. Nicotinic acetylcholine receptor (AChR) antibodies result in loss of AChRs and also directly block the function of the remaining AChR molecules, thereby causing a defect in neuromuscular transmission. The majority, though not all, of both myasthenic and non-myasthenic infants were found to have a repertoire of anti-AChR specificities very similar to their mothers. No significant differences were observed between sera from the two groups of mothers. Adequate treatment in mothers can reduce both frequency and severity of neonatal disease. Neonatal disease will recover following IVIg treatment (Béhin et al. 2008; O'Carroll et al. 2009). The absence of neonatal myasthenia gravis might be caused by the antigenic differences between the fetal and adult enzymes similar to those detected in rats (Hall et al. 1985; Hesselmans et al. 1993). The human fetal acetylcholine receptor (AChR) is present until 33 weeks gestation, when the fetal (γ) subunit is replaced by the adult (ε) subunit. The term "fetal acetylcholine receptor inactivation syndrome" has been proposed for the illness, when other developmental disorders were also caused by the maternal antibodies (Oskoui et al. 2008).

9.3.7 Neonatal Guillain-Barré Syndrome (GBS)

Neonatal Guillain-Barré syndrome (GBS) was observed to occur 7–12 days postpartum in children born to mothers with GBS. Serum from mother and infant depressed quantal content by approximately 90% and reduced the amplitude of postsynaptic currents by 30–40% in mouse, newborn and juvenile rats. The antibody nature of the blockade could be confirmed by showing that monovalent Fab fragments were similarly effective as purified immunoglobulin (Ig) G. Both cellular and humoral immune mechanisms are operative in Guillain-Barré syndrome (GBS). Transplacentally transferred blocking antibodies may be specifically directed at epitopes of the mature but not the fetal neuromuscular junction (Luijckx et al. 1997; Buchwald et al. 1998, 1999). Guillain-Barré syndrome and Sydenheim's chorea are diseases, which were shown to be associated with the immune response after microbial infections. The occurrence of Guillain-Barré syndrome noted in infants whose mother had harmless autoimmune antibodies during pregnancy (Buchwald et al. 1999; Sladky 2004). The syndrome's occurrence within families is also of interest. The MMP9 C(-1562)T and TNFA C(-863)A SNP were associated with severe weakness and poor outcome, indicating that these SNPs may be one of the factors predisposing to a severe form of GBS (Geleijns et al. 2007).

The associated features of ER22/23EK carriers consist of favorable metabolic and body compositional conditions. In contrast, the N363S polymorphism was reported to be associated with an enhanced sensitivity to glycocorticoids. Haplotypes carrying the minor allele of the *Bcl*I **polymorphism of the glycocorticoid receptor gene** was related to the phenotype and outcome of GBS explaining the family dependence of the syndrome and other neonatal disorders (Dekker et al. 2009).

9.3.8 Permanent Neonatal Diabetes Mellitus (PNDM)

Mutations in about a dozen of genes have been linked to the development of **Permanent Neonatal Diabetes Mellitus (PNDM)**. The most frequent causes of PNDM are heterozygous mutations in the *KCNJ11, INS and ABCC8* genes. Although PNDM is a rare phenomenon (one case in about 200,000 live births), this discovery has had a large impact on clinical practice as most carriers of KCNJ11 and ABCC8 gene mutations have been switched from insulin to oral sulphonylureas with an improvement in glycemic control (Aguilar-Bryan and Bryan 2008; Rubio-Cabezas et al. 2011).

9.3.9 Transient Neonatal Diabetes Mellitus (TNDM)

The majority **of transient neonatal diabetes mellitus (TNDM)** cases have an abnormality in chromosome 6q24. Half of the NDM cases are transient (TNDM) and the other most frequent causes of NDM are missense mutations in the

pancreatic β-cell K_{ATP} channel genes *KCNJ11, INS and ABCC8* (chr11), and in the preproinsulin gene, NDM has been linked to numerous other genetic causes including point mutations in GCK (chr7), GLIS3 (chr9), EIF2AK3 (chr2), PDX1 (chr13), PTF1A (chr10), SLC2A2 (chr3), HNF1B(chr17) or FOXP3 (chrX) (Aguilar-Bryan and Bryan 2008; Bonnefond et al. 2010). Genetic mutations were identified in ~75% of non-consanguinous probands with PNDM/MDI, using sequential screening of *KCNJ11, INS and ABCC8* genes in infants diagnosed within the first 6 months of age.

This percentage decreased to 12% in those with diabetes diagnosed between 7 and 12 months. Patients belonging to the latter group may either carry mutations in genes different from those commonly found in PNDM/MDI or have developed an early-onset form of autoimmune diabetes. Islet-cell antibodies (ICA), glutamic acid decarboxylase autoantibodies (GADA), tyrosine phosphatase-related proteins-islet antigen 2 autoantibodies (IA-2A), insulin autoantibodies (IAA), Zinc transporter 8 autoantibodies (ZnT8A) were found in the sera of the children, suggesting autoimmune origin of their disease (Russo et al. 2011).

9.3.10 Biliary Atresia (BA)

Biliary atresia (BA) is a devastating disease of infants, invariably leading to cirrhosis, end-stage liver disease, and death if untreated. It has been shown using microarray technique, that the T-cell regulatory gene RRAS seems to be a key factor in the development of the disease (Zhao et al. 2011). A recent review reported that BA may involve a primary perinatal hepatobiliary reoviral or rotaviral infection and a secondary autoimmune-mediated bile duct injury (Mack 2007). The maternal virus infections followed by maternofoetal microchimerism seems to be a very impressive explanation of the etiology (Muraji et al. 2008). In a mouse model, oral vaccination before mating with RotaTeq and Rotarix prevented most Rhesus Rotavirus-induced BA (Turowski et al. 2010). Biliary atresia is probably the end-result of different aetiological factors, among which viruses and other agents may cross the placenta. Otherwise it cannot be understand, why only one of the twins obtain the disease (Morris et al. 1977). The **anti-idiotypes transcytosed** by different efficiency into the circulation of the twins, might be an additional explanation for the asymmetric disease.

9.3.11 Maternal Symptomless Paraproteinemia

Maternal symptomless paraproteinemia was also found to be transmitted to the fetus. The paraprotein was detected after birth for 3 months in the serum of the child and caused prolonged immunosuppression without later consequences (Littlewood et al. 1970; Littlewood and Payne 1977).

9.3.12 *Acquired von Willebrand Syndrome (AVWS)*

Transient neonatal **acquired von Willebrand syndrome (AVWS)** has been observed peripartum. Its clinical management is analogous to monoclonal gammopathy of undetermined significance (MGUS) of the mother since it is the consequence of transplacental transfer of maternal IgG antibodies (Simone et al. 1968; Nageswara Rao et al. 2009).

9.3.13 *Fetal and Neonatal Alloimmune Thromocytopenia (FMAIT)*

Immune trombocytopenic purpura associated with pregnancy. **Fetal and neonatal alloimmune thromocytopenia (FMAIT)** results from transplacental transfer of maternal antibodies that develop in response to alloimmunization against paternal human platelet antigens (HPAs) expressed on fetal platelets. This thrombocyte loss could be prevented using modified IgG molecules (Ghevaert et al. 2008). At present seven biallelic human platelet antigen (HPA) systems have been determined and can be typed using genomic DNA. Platelet genotyping is a valuable tool in confirming platelet antigen specificities of alloantibodies detected in patients' sera to complement the clinical history in the diagnosis of alloimmune platelet disorders such as fetal and neonatal alloimmune thrombocytopenia (FNAIT). Prenatal platelet typing of the fetus in suspected cases of FNAIT became also available (Curtis 2008). Half of the infants were borne with low platelet counts and 6 of 16 required replacement therapy upon birth (Ozkan et al. 2010; Gasim 2011). The maternal, transplacental IgG binding to the fetal platelets was suggested to prevent their recirculation by FcγR binding to and phagocytosis by macrophages. The pathogenesis of immune trompcytopenic purpura and that associated to myelodysplasia and leukemia were shown to be different (Psaila and Bussel 2008; Psaila et al. 2011).

9.3.14 *Neonatal Endarteritis*

Neonatal endarteritis has been diagnosed in the newborns of mothers suffering from **endarteritis nodosa**. Fatal myocardial infarction in a neonate due to coronary arteries is compared with two lethal cases of Mucocutaneous Lymph Node Syndrome and/or Infantile Periarteritis Nodosa (MLNS/IPN). Cutaneous polyarteritis was transmitted to the newborn, too (Kitzmiller 1978; Krapf et al. 1981; Stone et al. 1993). During the last decade no publication could be found on neonatal endarteritis. Probably the pathogenesis of this disease has been reevaluated in the light of the molecular diagnostic findings.

9.3.15 Primary Immunodeficiencies

Hereditary autoinflammatory syndromes are caused by monogenic defects of innate immunity and are **classified as primary immunodeficiencies**. These syndromes are characterized by recurrent or persistent systemic inflammatory symptoms and must be distinguished from infectious diseases, autoimmune diseases, and other primary immunodeficiencies. The sited review describes the epidemiological, clinical and laboratory features, prognosis, and treatment of the main autoinflammatory syndromes, namely: familial Mediterranean fever; TNF receptor associated periodic syndrome; the cryopyrinopathies; mevalonate kinase deficiency; pediatric granulomatous arthritis; pyogenic arthritis, pyoderma gangrenosum and acne syndrome; Majeed syndrome; and deficiency of interleukin 1 receptor antagonist. The cryopyrinopathies discussed include neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurologic, cutaneous and articular syndrome), Muckle-Wells syndrome, and familial cold autoinflammatory syndrome (Jesus et al. 2010). Primary immunodeficiencies (PIDs) were analyzed to gain insight into the physiopathology of SLE. Some PIDs have been consistently associated with SLE or lupus-like manifestations: (a) homozygous deficiencies of the early components of the classical complement pathway in the following decreasing order: in C1q, 93% of affected patients developed SLE; in C4, 75%; inC1r/s, 57%; and in C2, up to 25%; (b) female carriers of X-linked chronic granulomatous disease allele; and (c) IgA deficiency, present in around 5% of juvenile SLE.

Mutations of the complement system (C1-inhibitor; C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8 and C9 deficiencies were shown to facilitate the development of SLE in addition to the facilitation of bacterial infections (C1 and C4, encapsulated bacteria; C5 to C9 Neisseria).

Other autoimmune diseases, i.e. polyendocrinopathy candidiasis ectodermal dystrophy (APECED), immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX), and autoimmune lymphoproliferative syndrome (ALPS), suggesting that mechanisms considered as critical players for induction and maintenance of tolerance to autoantigens, such as (1) AIRE-mediated thymic negative selection of lymphocytes, (2) $Foxp3^+$ regulatory T cell mediated peripheral tolerance, and (3) deletion of auto-reactive lymphocytes by Fas-mediated apoptosis, were not found to be associated with SLE physiopathology (Blois et al. 2007; Carneiro-Sampaio et al. 2008).

9.3.16 Behçet Syndrome (BS)

Behçet syndrome (BS) is a multisystem chronic inflammatory disorder, which is characterized by relapsing oral and genital ulceration and iridocyclitis. While being of unknown etiology, vasculitic changes of possible autoimmune origin are common to all involved organs, and thrombotic complications, which may adversely affect gestation, are frequently seen was shown to possess genetic etiology on the basis of the comparison of its incidence among monozygotic and dizygotic twins (Masatlioglu et al. 2010).

Pregnancy does not have a deleterious effect on the course of BD and may possibly ameliorate its course. However, it seems that BD may adversely affect pregnancy. The miscarriage rate was higher, and the pregnancy complications and cesarean section rates were significantly elevated (Jadaon et al. 2005). Overall, parity was associated with an 11% increased risk of female predominant autoimmune diseases. Pregnancies resulting in liveborn children therefore seem to contribute only little to the general female predominance in autoimmune diseases.

9.3.17 Crohn's Disease and Ulcerative Colitis

Crohn's disease and ulcerative colitis; In idiopathic inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, there is pathogenic build-up of $CD4^+$ T cells at sites of inflammation, mediated in part by IL-6, which provides (as described earlier) an anti-apoptotic signal to T cells through the induction of Bcl-2 and BclxL and promotes Th17 lineage differentiation. IL-17 is upregulated in patients with both types of IBD. IL-6 levels are elevated markedly in the serum of patients with IBD, decrease with treatment of inflammation and are predictive of IBD relapse. Microbial pattern-recognition receptors, such as the TLRs and NOD2 (nucleotide oligomerization domain 2), which activate NF-kB, have been implicated in these conditions. Neutralisation with an anti-IL-6R antibody largely prevented the colitis in mice (Arad et al. 2010).

Most women and men with **ulcerative colitis (UC) and Crohn's disease (CD)** can expect a healthy child with neither preterm birth nor low birthweight. No neonatal forms have been described (Ludvigsson and Ludvigsson 2002; Van Assche et al. 2005). Later Crohn's disease was shown to impair the fetal outcome in the case of the affected mothers (Naganuma et al. 2011).

Colitis-associated-cancer (CAC); TGF-β suppresses the formation of cancer by inhibiting IL-6 trans-signaling and human samples of colon cancer have low-levels of IL-6R, as do samples of inflamed colon. Adenomatous polyposis coli (APC) gene of mice with APC mutation develop cancer, genetic deletion of the TLR-adaptor protein MyD88 decreased the number of cancers markedly. Because MyD88 activation in turn activates NF-kB, it is not surprising that IL-6 production was decreased greatly in mice deficient in MyD88 and supports prior data showing that IL-6 is one of the effector signals in the TLR–NF-kB activation pathway (Becker et al. 2003). TGF-β was found to suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling.

9.3.18 Huntington Disease

Huntington disease was found to be of congenital origin, and the diagnosis can be obtained before implantation (HDCRG 1993; Peciña et al. 2010). The causal mutation is the expansion of a CAG trinucleotide repeat tract in exon 1 of a large

gene on chromosome 4 that results in the extension of a polyglutamine tract at the N-terminus of the encoded, ubiquitously expressed *protein called huntingtin*. From the maternal blood the DNA from the fetal-maternal transport can be also applied for the prenatal diagnosis (Bustamante-Aragones et al. 2008).

9.3.19 Hypoparathyroidism

Hypoparathyroidism with autoimmunity due to the 22q11.2 deletion syndrome. The majority of patients acquired autoimmune antibodies, but without anti-parathyroid antibodies (Lima et al. 2011).

9.3.20 Wegener Granulomatosis (WG)

Wegener granulomatosis (WG) is systemic disease of unknown etiology characterized by necrotizing granulomatous inflammation, tissue necrosis, and variable degrees of vasculitis in small and medium-sized blood vessels. The classic clinical pattern is a triad involving the upper airways, lungs and kidneys. Ninety percent of patients present with symptoms involving the upper and/or lower airways, and 80% will eventually develop renal disease (Mubashir et al. 2006). Pregnancy in patients with WG requires preconceptional planning, careful clinical management, and vigorous treatment of active disease. The management is individualized and the pregnancy outcome is variable. Antenatal management and therapeutic options are important (Koukoura et al. 2008). **No neonatal disease have been described**, and IVIg treatment could be successfully applied in the steroid resistant patients (Bellisai et al. 2004).

9.3.21 Kawasaki Disease (KD)

Kawasaki disease (KD) is an illness mostly of infants and young children, the majority being less than 4 years old. The peak age of onset of illness is 6–11 months. It is unusual in very young infants. From 1970 to 1995, only six instances of KD occurred in infants 30 days of age or younger in Japan, and infants 90 days of age or younger accounted for only 1.67% of all patients. The youngest infant of KD to date (a neonate 2 week old) was reported by Stanley and Grimwood. The youngest reported from India is a 46-day-old infant (Thapa et al. 2007).

9.4 Biological Therapy of Tumours and Autoimmune Diseases

Therapeutic monoclonal antibodies (mAbs) are most commonly of the IgG1 subclass, which is transported most efficiently to the fetus. In all animal species used for testing developmental toxicity, fetal exposure to IgG is very low during organogenesis, but this increases during the latter half of gestation such that the neonate is born with an IgG1 concentration similar to the mother. The therapeutic monoclonal antibodies might cause *developmental and reproductive toxicity* (DART) requiring testing of antibody-based therapeutics (Pentsuk and van der Laan 2009).

9.4.1 IVIg Treatment and Plasmapheresis During Pregnancy

Guillain-Barré syndrome during pregnancy can be also treated with IVIg and plasmapheresis. (Niklasson et al. 1998; Goyal et al. 2004; Bahadur et al. 2009; Modi et al. 2010; Ohlsson and Lacy 2010).

Polyclonal antisera, administered for passive immunization, are mixtures of different proteins, sharing binding activity against the antigen (Ag) determinants of the same immunogen preparation. Immunoadhesins (or immunoglobulin fusion proteins) are antibody-like molecules resulting from the fusion of a constant region (e.g., Fc portion) of an immunoglobulin and the ligand-binding region of a receptor or an adhesive molecule. Antibody fragments such as Fab, scFv, diabodies, and minibodies are molecules devoid of part or whole of the Fc portion. Therefore, they have faster clearance and better tissue/tumor penetration than whole immunoglobulins and they will perform better than whole IgGs in conditions where a short half-life is desirable, such as in radio-imaging and/or radio-therapy. They have no ADCC and CDC triggering activity. The smallest proteins retaining antigen binding are a single variable domain antibody (Nieri et al. 2009). IVIg prevention improves the risk of heart block of SLE patients (Friedman et al. 2010).

Several members of the idiotype-anti-idiotype network and antibody dimers including antigen-antibody complexes were found in the IVIg preparations (Luijten et al. 1988; Osterhaus et al. 1989; Clark et al. 2010).

9.4.2 Anti-idiotype Therapeutic Vaccines

105AD7 anti-idiotype monoclonal antibody can mimic the CD55 antigen. The molecular basis of 105AD7 mimicry has been identified with three CDR regions of 105AD7 showing similarity to three regions of CD55. These regions have been analysed for potential T-cell epitopes, and sequences that are predicted to bind to HLA/A1,3,24 and to HLA/DR1,3,7 have been identified within the CDRH3 region of 105AD7. 105AD7 can stimulate CD4 and CD8 responses in colorectal cancer

patients with the appropriate haplotype. Only a few patients produce a sustained memory response (Durrant et al. 2000; Reinartz et al. 2003). Most of these vaccines for the lymphoma therapy use the tumor B cell idiotype (the unique variable region of the surface immunoglobulin) as a tumor-specific antigen. In spite of several problems anti-idiotype vaccines prospect towards integration of this strategy in the therapeutic armamentarium for lymphoma (Houot and Levy 2009). Clinical studies have been published using different preparations and summarised at the end of Table 9.1.

9.4.2.1 Therapeutic Monoclonal Antibodies and Their Potential Effects on the Developing Fetus

Abagovomab (ACA125) acts as an antigen mimic of the carbohydrate ovarian cancer antigen 125 (Wagner et al. 1997). The frequency of peripheral T_{REG}s was increased during abagovomab therapy in a high percentage of patients. Despite higher T_{REG} counts compared with baseline levels, the suppressive capacity of T_{REG}s was reduced in a subset of patients. The data further indicate that the ability of T cells to proliferate in response to CA-125 *in vitro* could be associated with diminished T_{REG} activity. Importantly, CA-125–specific immunity could not be enhanced by *in vitro* T_{REG} depletion, as CA-125 induced $CD25^+$ $FoxP3^+$ T_{REG}s with suppressive capacity.

Abatacept (Orencia) Human IgG Fc domain 1 CTLA-4; anti-CD80 and anti-CD86.

Abatacept (ABT, Orencia, Bristol-Myers Squibb Ltd) Rheumatoid arthritis tumor necrosis factor inhibitor in phase 3 clinical trial, but it was found effective only in very early phase of the disease (Malottki et al. 2011; Emery et al. 2010). Prophylactic withdrawal of drugs before pregnancy is mandatory (Østensen et al. 2008). At present reports on abatacept, tocilizumab or anakinra are inconclusive therefore throughout pregnancy cannot be recommended (Østensen and Förger 2011).

Abciximab (ReoPro) IgG1κ-Fab, chimera – integrinα2β3 (platelet-GP) – haemostasis/trombosis (Nieri et al. 2009). Using immunohistochemistry, ReoPro was only detected attached to maternal and fetal platelets, and to the trophoblastic surface of the placental villi (Miller et al. 2003a, b). The effect of Abciximab to ICAM-1 was excluded, but an effect to monocytes could not be excluded (Voisard et al. 2006).

Adalimumab (ADA, Humira; Abbott) Human recombinant, IgG1κ, anti-TNFα, AS, PsA, CD, PP, JIA (van Schouwenburg et al. 2010) TNF-alpha blocker therapy (adalimumab). The therapy of pregnants showed no increase in miscarriage, prematurity or structural malformations in neonates compared with non-exposed pregnancies (Østensen et al. 2008). Expression of HLA-G on PMBCs is up-regulated in ankylosing spondylitis (AS), correlates with acute phase reactants and decreases after TNF-alpha blocker therapy (Chen et al. 2010). Anti-TNFα is used for the treatment of infectious bowel diseases even during pregnancy, which might influence the development of the fetal immune system (Arsenescu et al. 2011). **Anti Adalimumab anti-idiotype** Antibodies (Bartelds et al. 2007, 2010; Malottki et al. 2011; Nieri et al. 2009).

Table 9.1 Groups of therapeutic monoclonals according to the target molecules and fetal effects

Specification	Specificity	References	Fetal consequences
Abagovomab	(ACA125) ovarian cancer antigen 125	Wagner et al. (1997)	?
Siplizumab	anti-CD2, ADCC	Fanale and Younes (2007)	?
Muromonab	anti-CD3 t.1 diabetes	Chatenoud and Bluestone (2007)	?
Teplizumab	anti-CD3 t.1 diabetes	Herold et al. (2002, 2005)	?
Visilizumab	anti-CD3 Crohn's d	D'Haens and Daperno (2006)	?
Blinatumomab	EpCam cc CD3/CD19	Houot et al. (2011)	?
Catomaxomab	EpCam anti CD3	Foon et al. (1999)	?
Edrecolonab	EpCam cdc-ADCC-cc	Nieri et al. (2009)	?
Retuximab	a-CD20 HCV cryogl.	Sodani et al. (2010)	?
Rituximab	a-CD20 Burkitt's ly.	Friedrichs et al. (2006), Rak et al. (2009), and Gall et al. (2010)	Fetal B-cell depletion, maternal bleeding, reduced microchimerism
Tositumomab	a-CD20 B-cell lymph.	Armstrong and Eck (2003)	?
TriGerm	a-CD20(glicoside GD2)	Nieri et al. (2009)	?
Veltuzumab	a-CD20 (Rituximablike)	Watanabe, (2011)	?
LFB-R603	a-CD20, B cell malign.	Urbain et al. (2009)	?
^{90}Yttrium-ibritumomab tiuxetan	anti-CD20	Watanabe (2011)	?
^{131}Iodine-rituximab	anti-CD20	Watanabe (2011)	?
Epratuzumab	a-CD22 B-cell lymph.	Leonard et al. (2008)	?
Inotuzumab	anti-CD22 (CMC-544)	Clowse (2010)	?
Basiliximab	a-CD25/IL2R-antagon.	Aktas et al. (2011) (−10% bw)	Pentsuk and van der Laan (2009)
Daclizumab	a-DC25 IL2R-antagon.	Elimelakh et al. (2007)	?
Iratumumab	a-CD30 (Hodgkin's ly.)	Klimm et al. (2005)	?
Gemtuzumab	a-CD33 (drug targeting)	Nieri et al. (2009)	?
A-CD34, CD105	non-small cell lung cc	Tanaka et al. (2001)	?
Dacetuzumab	a-CD40 (TNF-receptor)	Houot et al. (2011)	?
Alemtuzumab	anti-CD52 anti-Ca125	Elimelakh et al. (2007)	Lim et al. (2008)
Onercept	anti-p55 soluble TNFR	Bosani et al. (2009)	?
Abatacept	a-CD80 and anti-CD86	Malottki et al. (2011) (NONE)	Østensen et al. (2008), Emery et al. (2010), and Østensen and Förger, (2011) None
Galiximab	a-CD80 (follic. lymph)	Watanabe, (2011)	?
Tocilizumab	a-CD128 IL-6R α-chain	Sato et al. (1993)	MMP inhibition, PPRM
anti-CD137	TNF receptor (a.4-1BB)	Houot et al. (2011)	?
Belatacept	CTLA4-Ig (tolerogenic)	Kaufman et al. (1999)	Bahri et al. (2009) sHLA-G+

(continued)

Table 9.1 (continued)

Specification	Specificity	References	Fetal consequences
Ipilimumab	CTLA4-Ig (CD152)	Nieri et al. (2009)	Houot et al. (2011)?
Tremelimumab	CTLA4-Ig (CD152)	Houot et al. (2011)	?
Abciximab	Integrin α2β3 (platelet)	Nieri et al. (2009)	Miller et al. (2003a, b), Voisard et al. (2006)
Efalizumab	a-integrin-CD11a	Nieri et al. (2009)	?
MLN-02	anti-α4β7 integrin	Bosani et al. (2009)	?
Natalizumab	anti-α4-integrin (SM)	Pentsuk and van der Laan (2009)	>abortion, >stillbirth rate
Adalimumab	anti-TNFα	van Schouwenburg et al. (2010)	Østensen et al. (2008) +, Winger and Reed (2008) +, Chen et al. (2010) +, Arsenescu et al. (2011) +, and Schnitzler et al. (2011) +
Certolizumab	a-TNF-α (RA and CD)	Østensen and Förger (2011)	?
Etanercept	anti-TNFα	Clowse (2010)	Rak et al. (2009) < microchimerism
Golimumab	anti-TNFα	Østensen and Förger (2011)	Lee et al. (2005) – ?
anti-leu-2	T-subpopulation marker	Champlin et al. (1990)	?
Apomab	TRAIL(DR5/TNF-R)	Nieri et al. (2009)	?
Mapatumumab	TRAIL(DR5/TNF-R)	Nieri et al. (2009)	?
Bavituximad	a-phosphatidylserine	He et al. (2009) glioma, HCV	Quer et al. (2010) ?
Bevacizumab	anti-VGEF-A (colorectal cc)	Nieri et al. (2009) and Pentsuk and van der Laan (2009)	Csáky and Do (2009); Petrou et al. (2009) fetal loss
Ranibizumab	anti-VEGF-A (angiogenesis inhibitor.)	Ferrara et al. (2003, 2006)	?
Ramucirumab	VEGFR2 (angiogenesis inhibitor)	Krupitskaya and Wakelee (2009)	?
Cetuximab	anti-EGFR (HER-1) cc	Powell et al. (2008) and Rech and Vonderheide (2009)	Fetal weight loss
Matuzumab	anti-EGFR	Seiden et al. (2007)	?
Necitumumab	a-EGFR-1/HER-1(cc)	Kuenen et al. (2010)	?
Nimotuzumab	anti-EGFR-1/HER-1 (apoptosis)	Quatrale et al. (2011)	?
Panitumumab	anti-EGFR colorectal cc	Pentsuk and van der Laan (2009)	>abortion, >fetal death
Trastuzumab	anti-HER2, Erb-B2, ADCC-CDC	Matsumoto et al. (2009) and Sukumvanich (2011)	Reversible anhydramnion

(continued)

Table 9.1 (continued)

Specification	Specificity	References	Fetal consequences
Zalutumumab	anti-EGFR complement lysis	Klausz et al. (2011)	?
Cixutumumab	Insulin-like GFR (IGF-IR)	Bouché et al. (2005), McKian and Haluska, (2009), and Quatrale et al. (2011)	Maternal hyperglycemia ?;
CNTO-328	Human IL-6 specific	Voorhees et al. (2009)	?
CT-011	anti PD-1 (programmed cell death)	Houot et al. (2011) and Mkrtichyan et al. (2011)	?
Eculizumab	a-complement factor 5	Thomas et al. (1996) and Kelly et al. (2010)	Inocuous
TriAb 11D10	Breast cancer	Reece et al. (2000, 2001, 2003)	?
Fontolizumab	anti RSV (prevention)	Nieri et al. (2009) and Reinisch et al. (2010)	Pediatric treatment, not tested
Motavizumab	anti RSV (prevention)	Nieri et al. (2009), Weisman (2009)	Pediatric treatment, not tested
Palivizumab	anti RSV (prevention)	Martin-Mateos, (2007) and Nieri et al. (2009)	Pediatric treatment, not tested
LFB-R593	anti-RhD human MAb	Urbain et al. (2009)	Not tested
Omalizumab	anti-IgE (asthma ther.)	Corren et al. (2009)	Not tested yet
Infliximab	**Anti-idiotype** (TNF-α); (RA, Crohn's disease)	Bartelds et al. (2010) and Clowse (2010)	Fertility reduction; high fetal a-TNFα
Anti-adalimumab	**Anti-idiotype** (TNF-α)	Nieri et al. (2009) and Bartelds et al. (2007)	?
MELIMMUNE	**a-idiotype**, melanoma	Pride et al. (1998)	Murray et al. (2004) ?
Mitumomab	**a-idiotype** (GD3 ganglioside)	Giaccone et al. (2005) and Bottomley et al. (2008)	?
Racotumomab	**Anti-idiotype** (N-glycolyl-GM3 ganglioside)	Guthmann et al. (2006)	?
Anti-Trastuzumab	**Anti-idiotype (vaccine)**	Kulkarni et al. (2010) and Sukumvanich (2011)	Anhydraminon

Abbreviations: ?/? not tested, or inconclusive results, +, not recommended during pregnancy, *sHLA-G+* increased concentration of soluble HLA-G, *< bw* reduced birth weight, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *PsA psoriatic arthritis*, *CD* Crohn's disease, *UC* ulcerative colitis, *PP* plaque psoriasis, *JIA* juvenile idiopathic arthritis, See other abbreviations in the list

Direct exposure to anti-TNF treatment during pregnancy was not related to a higher incidence of adverse pregnancy outcomes than infectious bowell diseases overall (Schnitzler et al. 2011). The anti-TNF agent was started prior to conception and continued until there was evidence of fetal cardiac activity. In women treated with a combination of anti-TNF therapy, anticoagulation therapy, and IVIg, the live birth rates (71%) were greater than those in women treated with anticoagulation therapy alone (19%) or in those receiving a combination of anticoagulation therapy and IVIg (54%). Fetal outcomes, including gestational age and birth weight, were similar across the groups, and no congenital anomalies were reported after anti-TNF agent exposure (Winger and Reed 2008; Vinet et al. 2009).

Rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn's disease (Østensen and Förger 2011). All users requested at least one time repeatedly the treatment in Norway (Mahic et al. 2011). Long term treatment did not resulted in reactivation of chronic hepatitis B virus infection (Mori 2011). The treatment caused the improvement in two bone formation markers – β-alkaline phosphatase and osteocalcin (Veerappan et al. 2011).

Alemtuzumab (MabCampath, Genzyme) Humanized, IgG1k, anti-CD52 anti-CA125 immunoglobulin directed against CD52 antigen expressed on T-and B lymphocytes, monocytes, macrophages, NK cells, and a subpopulation of granulocytes, but not on hematologic precursors. Induction of CDC or ADCC on an FcReceptor γ-binding mechanism.

Pancreas transplant recipients on alemtuzumab maintenance therapy suffered frequently from red cell aplasia, and autoimmune hemolytic anaemia. (Elimelakh et al. 2007) Cord-blood-hematopoetic-stem-cell expansion and increase the availability of cord-blood units for transplantation (Lim et al. 2008). In contrast to IVIg and Rituximab the compound may be an effective therapy for complex immunohematologic disorders complicating hematopoietic stem cell transplantation. The paper emphasizes the importance of T-cells in transplant associated immune cytopenias (Chao et al. 2008). B-CCL (Nieri et al. 2009).

Alicaforsen is a human monoclonal antibody α1β2-integrin, also known as leukocyte function antigen (LFA)-1, and its ligand, intercellular adhesion molecule-1 (ICAM-1), is important for the recruitment of leukocytes to inflammatory sites (Bosani et al. 2009).

Anti-CD34 and anti CD105 intratumoral microvessel density (IMVD) monoclonal antibodies. Anti-CD105 was more effective against non-small cell lung cancer than anti-CD34 (Tanaka et al. 2001).

Anti-CD137 mAb (BMS-663513, Bristol-Myers Squibb) 4-1BB (CDw 137), a member of tumor necrosis factor receptor (TNFR) superfamily stimulating T-cells, NK-cells and DCs (Houot et al. 2011). anti-CD137 mAb enhances rituximab-dependent cytotoxicity against the lymphoma cells (Lee et al. 2005; Kohrt et al. 2011).

Anti-leu-2b or anti-Leu-2c, IgG2a, marker of T-cell subpopulation (Clement et al. 1984; Champlin et al. 1990).

Apomab (Genentech) IgG1, against extracellular domain DR5/tumor necrosis factor related (TRAIL) receptor 2 apoptosis inducing ligand (Nieri et al. 2009).

Basiliximab (Simulect) Chimeric, IgG1κ, anti-CD25, IL2R antagonist (Aktas et al. 2011) 10% reduced fetal body weight (Pentsuk and van der Laan 2009).

Bavituximab (Peregrine Pharmaceuticals, Inc., Tustin, CA), anti-phosphatidylserine Bavituximab combined with radiotherapy holds promise as a vascular targeting and immune enhancement strategy for the treatment of human glioblastoma (He et al. 2009). HCV therapy (immunostimulant) (Dammacco et al. 2010; Quer et al. 2010).

Belatacept (CTLA4-Ig) is a new recombinant molecule that interferes with the signal of T lymphocyte activation and prevents acute rejection after renal transplantation. HLA-G acts as a naturally tolerogenic molecule in humans. Patients treated with CTLA4-Ig displayed significantly higher soluble HLA-G (sHLA-G) plasma concentrations than patients treated with calcineurin inhibitors or healthy donors (Bahri et al. 2009).

CTLA4-Ig-treated DC acted as tolerogenic APC through sHLA-G secretion as they suppressed T cell alloproliferation, which could be restored by using a neutralizing anti-HLA-G Ab (Bahri et al. 2009). The use of anti tumour necrosis factor MABs are not recommended (Partlett and Roussou 2011). Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a negative regulator of T cell activation and may modulate peripheral self-tolerance (Kaufman et al. 1999).

Bevacizumab (Avastin) Humanized, IgG1κ, anti-vascular endothelial growth factor-A (VEGF-A) used for the treatment of non-small cell lung cancer, (NSCLC) colorectal cancer (CC); (Nieri et al. 2009).

EFD rabbit: dose-dependant decrease in maternal bodyweight, increase in fetal malformations and late resorptions; (Pentsuk and van der Laan 2009). Intravitreal bevacizumab therapy during pregnancy for off-label ocular indications can result in significant visual improvement without adverse fetal events related to treatment (Tarantola et al. 2010).

Intravitreal 1.25 mg bevacizumab may reach the systemic circulation in plasma concentrations of 100 ng/mL (Csáky and Do 2009). Two pregnants have lost their babies within 10 days following intravitreal injections of bevacizumab (Petrou et al. 2009). Placenta GF levels are elevated in the plasma of colorectal and rectal carcinoma patients receiving bevacizumab (Xu and Jain 2007). Prevention of angiogenesis by MSC in pancreatic cancer (Beckermann et al. 2008).

Blinatumomab (EpCam, antigen – Epithelial cell-adhesion molecule, – present on 85% of cancer cells) and MT-103 and MT110 present on all non-Hodgin lymphoma cells (Armstrong and Eck 2003; Nieri et al. 2009). CD3/CD19 bispecific, single chain recombinant antibody (Houot et al. 2011; Topp et al. 2011).

Catomaxomab (Removab) bifunctional recombinant anti epidermal cell adhesion molecule EpCam and anti-CD3. It is inducing ADCC in ovarian and stomach cancer. EpCam is the ligand for human leukocyte immune-globulin like receptor (LAIR-1) (Armstrong and Eck 2003; Nieri et al. 2009; Bokemeyer 2010; Rüssel et al. 2011).

CeaVac (mimicking carcinoembryonic antigen) colon cc (Foon et al. 1999).

Certolizumab (Cimzia®; UCB) Pegylated humanized antibody Fab' fragment of TNF-α monoclonal antibody; RA, CD; (Østensen and Förger 2011). Certolizumab does not cross the placenta as easily as the IgG derived drugs due to the pegylation

of the molecules, thus reducing the harmful consequences to the fetus (Clowse 2010).

Cetuximab (Erbitux) Chimeric, IgG1k, anti-epidermal growth factor receptor-1 (HER-1), apoptosis, CDCC colorectal cancer (CC); squamous cell cancer of head and neck (SCCHN) Weight loss and reduced food consumption in high-dose group Dose-dependent increase in abortion rates (not known, if could be associated with treatment) Weight loss and reduced food consumption in high-dose group (Powell et al. 2008; Pentsuk and van der Laan 2009; Rech and Vonderheide 2009).

ChAglyCD3 (CD3-specific) a humanized antibody, an aglycosylated human IgG1 antibody directed against CD3 was shown to reduce the insulin-requirement of the patients. Residual beta-cell function was better maintained with ChAglyCD3 than with placebo (Keymeulen et al. 2005).

Cixutumumab (IMG-12 or CIX) targeting insulin-like growth factor receptor (IGF-IR) treatment for multiple cancers. Human IgG1, blocks interaction between IGF-IR and its ligands, IGF-I and -II, and induces internalization and degradation of IGF-IR. Its combination of cetuximab (mAb against EGFR) inhibited the growth of pancreatic cancer and promoted its regression. An antiangiogenic mechanism was associated with CIX treatment. Reviewed recently (Quatrale et al. 2011). Hyperglycemia is a regular side effect, but the fetal consequences during pregnancy have not been evaluated yet (McKian and Haluska 2009). Eyelash trichomegaly in adults (Bouché et al. 2005; Garrido et al. 2007).

CNTO 328 Chimeric monoclonal antibody with high affinity for human IL-6 Myeloma multiplex sensitivity to glycocorticoid (Voorhees et al. 2009).

CT-011 (Curetech) humanized anti-PD-1 IgG1 mAb that binds to mouse and human PD-1, programmed death receptor 1. PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. (Houot et al. 2011; Mkrtichyan et al. 2011; Stagg et al. 2011; Wafula et al. 2009).

Dacetuzumab (SGN-40; Seattle Genetics) humanized; and HCD122 fully human (Novartis/XOMA); CD40, tumour necrosis factor receptor; B-cells, DCs, macrophages lymphomas (Houot et al. 2011).

Daclizumab (Zenapax) Humanized, IgG1κ, anti-α-chain of CD25, IL-2R antagonists (Elimelakh et al. 2007; Aktas et al. 2011) transplant rejection.

Eculizumab (Soliris) Humanized, IgG2/4j, anti-human complement C5; Paroxismal nocturnal haemoglobinuria (PNH); (Thomas et al. 1996; Nieri et al. 2009; Danilov et al. 2010). There was no evidence of complement blockade from cord blood samples taken at delivery. Eculizumab appears safe to use in this setting and is likely to prevent many of the complications usually observed (Kelly et al. 2010).

Edrecolomab (Panorex) IgG2a, EpCam antigen CDC-ADCC cancer (Nieri et al. 2009).

Efalizumab (Raptiva) Humanized, IgG1κ, anti-integrin-CD11a – Psoriasis (Nieri et al. 2009). Progressive multifocal leukoencephalopthy was found to be a rare, but lethal disease associated with long term efalizumab therapy (Kothary et al. 2011).

Epratuzumab, a humanized IgG1 unconjugated anti-CD22 antibody effective against non-Hodgkin lymphoma and follicular lymphoma (Leonard et al. 2008; Watanabe 2011). Consequences of the application during pregnancy has not been reported.

Etanercept (ETN, Enbrel, Wyeth Pharmaceuticals) Human IgG Fc domain 1 TNFR2/p75; anti-TNFα AS, PsA, PP, JIA; 81 ng/mL cord blood. 21 ng/mL 1 week postpartum 2 ng/mL; 3 weeks postpartum; undetectable 12 weeks postpartum (Clowse 2010). Reduction of post-partum microchimerism (Rak et al. 2009). Complications of the therapy may be acute anterior uveitis (etanercept), psoriasis (infliximab > etanercept) and infectious bowel disease (IBD) (etanercept > infliximab) which were observed in association with the treatment using TNF-antagonists. The paradoxical consequences, however, affected less than 5% of the treated patients (Fouache et al. 2009).

Eternacept, which is a recombinant human p75 soluble receptor to TNF, failed in a phase II trial with Crohn's disease and the trial was discontinued. The recombinant receptor proved to be useful for the treatment of rheumatoid arthritis (Malottki et al. 2011), but its use in pregnants has not been approved (Østensen et al. 2008). Etanercept treatment (25 mg × 2/week) has been stopped 6 weeks before pregnancy. The treatment had to be reinitiated from the 20th week of pregnancy and no fetal complication was observed (Umeda et al. 2010). The etanercept treatment was initiated 7 weeks before pregnancy (25 mg/sq-m 2 × weekly). The cord blood contained 81 ng/mL etanercept in contrast to the maternal serum (3,849–2,849 ng/mL). No detectable etanercept was found in the newborn's blood 12th week after delivery, although the breast milk contained 3.5 ng/mL etanercept (Murashima et al. 2009). All patients requested at least one times the repetition of the treatment according to a publication from Norway (Mahic et al. 2011).

Fontolizumab used for the preventive treatment of newborns at risk for respiratory syncytial virus infection (RSV) resulted a significant decrease in C-reactive protein levels suggested a beneficial biological effect. (Nieri et al. 2009; Reinisch et al. 2010).

Galiximab, a human-primate chimeric anti-CD80 antibody: Galiximab is a human-primate chimeric anti-CD80 antibody with excellent tolerability and single-agent effectiveness for recurrent follicular lymphoma (FL), resistant to other therapeutical means (Watanabe 2011).

Gemtuzumab (Mylotarg$^{\kappa}$) IgG4κ; humanised; CD33-monocyte, myeloid cell drug targeting (Nieri et al. 2009).

Golimumab (Simponi®; Centocor Ortho Biotech) Human monoclonal IgG1 antibody RA, AS, PsA (Østensen and Förger 2011).

HCD122 (Novartis/XOMA) CD40-specific fully human IgG1 mAb with antagonistic activity that mediates ADCC and blocks CD40L-induced survival and proliferation of normal and malignant B cells (Chatenoud and Bluestone 2007).

Ibritumomab tiuxetan (Zevalin) Murine, IgG1κ, anti-CD20; radiol (Yttrium 90) IMC-C225 (Nieri et al. 2009).

Infliximab (IFX, Remicade, Schering-Plough Ltd) Chimeric, IgG1κ, anti-tumor necrosis factor alpha (TNFα) Rheumatoid arthritis (RA) and Crohn's disease (CD) (Saleem et al. 2008; van Schouwenburg et al. 2010). Fatal case of disseminated mycobacterial infection has been reported in an infant who received BCG vaccine at 3 months of age. The mother had been treated with infliximab throughout her pregnancy. Vaccination with live bacteria and viruses should be postponed in infants exposed to infliximab *in utero*, until serum levels are undetectable which may require more than 6 months (Djokanovic et al. 2011). The fetal concentration of infliximab was found to be higher than that of the mother. This might be a risk for the postnatal development of the immune system (Zelinkova et al. 2011). Due to the high rate of IgG transfer near term, babies have been found to have similar blood levels of infliximab to their mothers (Clowse 2010). All reported pregnancy outcomes under treatment with infliximab showed no increase in miscarriage, prematurity or structural malformations in neonates compared with non-exposed pregnancies (Østensen et al. 2008). Only the chimeric monoclonal anti-TNF antibody infliximab is currently available worldwide. The potency of this agent in moderate-to-severe ulcerative colitis (UC) and CD has been one of the most important advances in the care of inflammatory bowel disease (IBD) in the past decade (D'Haens and Daperno 2006).

Anti-Infliximab anti-idiotypes. No association was found between the patients' allotypes and the presence or concentration of anti-infliximab antibodies (Bartelds et al. 2010) Reduction in fertility (not known, whether related with male or female animals) (Pentsuk and van der Laan 2009). VACTERL association? Acute Graft versus Host Disease (Couriel et al. 2009) were described, but it proved to be useful for the treatment of rheumatoid arthritis (Malottki et al. 2011).

Inotuzumab ozogamicin (CMC-544), the calicheamicin-conjugated anti-CD22 monoclonal antibody and rituximab combination were used for the treatment of ankylosing spondilitis, psoriatic arthritis and ulcerative colitis; (Nieri et al. 2009; Smith et al. 2010) the concentration in the blood of the newborn was 39.5 μg/mL 6 week post-partum and slowly declined over 6 months (Clowse 2010).

Ipilimumab (FcγRIIb binding) overcoming TCLA-4-mediated immunosuppression, increasing anticancer immune-response (melanoma malignum; MDX-010; Bristol-Myers Squibb/Medarex); CTLA-4 (CD152) T cells; T_{REG} cells; colon and prostatic cancer; (Nieri et al. 2009; Houot et al. 2011).

Iratumumab (SGN-30 and MDX-060) CD30-specific IgG used for the treatment of Hodgkin's lymphoma. Myelosuppression, fatigue, elevated liver enzymes were documented during therapy (Klimm et al. 2005).

LFB-R593, a fully human anti-rhesus D (RhD) antibody, for the prevention of feto-maternal allo-immunization in RhD- women, as a substitute for human polyclonal anti-RhD immunoglobulins (Urbain et al. 2009).

LFB-R603, a monoclonal antibody directed against CD20, for the treatment of B cell malignancies. Antibody-dependent cellular cytotoxicity (ADCC) activity and enhanced affinity to FcgRIII (CD16), both correlated to a glycosylation pattern characterized by a low fucose content (Urbain et al. 2009).

Mapatumumab; TRAIL receptor activation (death receptor 4) mediator of apoptosis in cancer cells (Nieri et al. 2009).

Matuzumab (humanised anti-EGFR monoclonal antibody; reviewed by Seiden et al. 2007; and recently by Quatrale et al. 2011).

MELIMMUNE: anti-idiotype antibody that mimic the high molecular weight chondroitin sulfate proteoglycan antigen of melanoma cells (Pride et al. 1998; Murray et al. 2004; Ward et al. 2011).

Mitumomab (Bec2, ImClone Systems) BEC-2 anti-idiotype (Giaccone et al. 2005; Bottomley et al. 2008) Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside that is expressed on the surface of tumor cells and is of neuroectodermal origin. Ganglioside GD3 can be used as a vaccine against small cell lung cancer (SCLC) (Nieri et al. 2009).

MLN-02 anti-α4β7 integrin antibody of IgG1 type, humanised (Reviewed by Bosani et al. 2009) approved for the treatment of Crohn's disease.

Motavizumab (Humanised mouse monoclonal antibody). Motavizumab targets a highly conserved epitope in the A antigenic site of the RSV fusion (F) protein, which is important in the invasion of RSV from cell to cell. Motavizumab, which differs from palivizumab by just 13 amino acids, has exhibited a 70-fold enhancement in binding to the RSV F protein compared with the first-generation mAb, with an 11-fold faster association rate and sixfold slower disassociation rate (Nieri et al. 2009; Weisman 2009).

Muromonab, IgG2a, Murine, T-cell CD3 blocade. CD3-specific monoclonal antibodies can re-establish immune homeostasis in treated individuals. This occurs through modulation of the T-cell receptor (TCR)–CD3 complex (also termed antigenic modulation) and/or induction of apoptosis of activated autoreactive T cells, which leaves behind 'space' for homeostatic reconstitution that favours selective induction, survival and expansion of adaptive regulatory T cells establishing long-term tolerance. It is used for early treatment of diabetes type 1 (Chatenoud and Bluestone 2007; Nieri et al. 2009).

Natalizumab (Tysabri) Humanized, IgG4κ, anti-α4-integrin (VLA-4), in the treatment of sclerosis multiplex (van Schouwenburg et al. 2010). Natalizumab blocks both alpha-4 B1 integrin (VCAM 1) and alpha-4β7 integrin (MADCAM 1) interactions (Rutgeerts et al. 2009). Therapy of sclerosis multiplex will be more efficient in combination with interferon (Miller et al. 2003a, b; Nieri et al. 2009).

In animal experiments EFD G. pig: reduced pregnancy rates in high-dose group; PPND Cyn: increased abortion and stillbirth rates (Pentsuk and van der Laan 2009). In cynomolgus monkeys, however, the abortion rate had not been increased, but hematopoetic changes were observed. Natalizumab had no adverse effects on the general health, survival, development, or immunological structure and function of infants born to dams treated with natalizumab during pregnancy (Wehner et al. 2009a, b). 10% of Natalizumab therapy has been stopped because of pregnancy. Three of 363 patients treated at least for 24 months developed progressive multifocal encephalopathy (PML; Piehl et al. 2011). The PML induction has been documented after natalizumab therapy of Crohn's disease first in 2005 (Kleinschmidt-DeMasters and Tyler 2005; Sandborn et al. 2005; Van Assche et al. 2005; Edula and Picco 2009).

Necitumumab (IMC-11F8) anti-EGFR human monoclonal antibody (Kuenen et al. 2010).

Nimotuzumab (theracim) humanised, anti-EGFR-1/HER-1; apoptosis, ADCC; head and neck cancers (HNCC), (Spicer 2005; Nieri et al. 2009; reviewed recently by Quatrale et al. 2011).

Omalizumab (Xolair) Humanized, IgG1κ, anti-IgE – asthma. Causing marked reduction in serum levels of free IgE and down-regulation of IgE receptors on circulating basophils. Effective in monozygotic twins (Holgate et al. 2005; Just et al. 2007; Nieri et al. 2009) tolerability (Corren et al. 2009).

Onercept, is a recombinant human p55 soluble receptor to TNF, failed in a phase II trial with Crohn's disease and the trial was discontinued (Bosani et al. 2009).

Palivizumab (Synagis) Humanized, IgG1κ, anti-respiratory syncytial virus "A" epitope of fusion protein. It is used for the prevention of respiratory syncytial virus infection of newborns with different risks for respiratory infections (Martin-Mateos 2007; Nieri et al. 2009; Weisman 2009).

Panitumumab (Vectibix) Human, IgG2κ, anti-human epidermal growth factor receptor binding the catalytic kinase domain of the receptor of colorectal cancer (CC; Nieri et al. 2009). Increased frequency of abortion/fetal death rates were observed in high-dose group (reviewed by Pentsuk and van der Laan 2009; Nieri et al. 2009). Eyelash trichomegaly in adults were seen (Zhang et al. 2007; Morris et al. 2011).

Racotumomab(1E10), an anti-idiotypic vaccine **mimicking the N-glycolyl-GM3 ganglioside** (Guthmann et al. 2006; Hernández et al. 2008) effective against breast and lung cancers. NGcGM3 is practically undetectable in healthy human tissues as a result of an Alu-mediated inactivation of the gene, the ganglioside is highly expressed in several human cancer cells presumably due to incorporation of dietary NGc (Fernandez et al. 2010).

Ramucirumab (DC-101) (an antibody to the VEGF receptor-2) (Tonra et al. 2006; Krupitskaya and Wakelee 2009).

Ranibizumab (Lucentis, Genentech) Humanized, IgG1-Fab, anti-human vasc. endothel. growth factor-A (VEGF-A); for the treatment of choroidal neovascular (wet) age-related macular degeneration (ARMD) reviewed recently (Ferrara et al. 2003, 2006); neovascular acute myeloid leukemia (neovascular-AML); (Csáky and Do 2009; Nieri et al. 2009).

Retuximab (Epstein-Barr Virus) anti-CD-20 (Sodani et al. 2010).

Rituximab (RTX, Mabthera$^{\kappa}$, Roche) Chimeric, IgG1κ, anti-CD20 (Sulesomab, Leukoscan). Murine Fab, binds to surface granulocyte non-specific crossreacting antigen present on neutrophils. Rhinitis, fever, chills and toxic laboratory findings occurred during the treatment (Klimm et al. 2005). HCV cryoglobulinaemia could be also treated (Dammacco et al. 2010). The treatment of pregnants because of Bukitt's lymphoma resulted high rituximab concentrations and a transient complete B-cell depletion in the cord blood. B-cell recovery was fast, showing a regular immunophenotype without loss of CD20 antigen, no functional deficits and adequate vaccination IgG titers (Friedrichs et al. 2006). Administration in third

trimester of pregnancy suppresses neonatal B-cell development, but without later neonatal consequences (Klink et al. 2008), in spite of these the prophylactic withdrawal has been recommended before pregnancy (Østensen et al. 2008).

Human fetal B-cell depletion and lymphocytopenia in *Cynomolgus*, were observed, too (Vaidyanathan et al. 2010). Reduction of post-partum microchimerism was documented (Rak et al. 2009). Useful in rheumatoid arthritis therapy (Malottki et al. 2011) in combination with chemotherapy depending on human concentrative nucleotide transporter 1 (hCNT1) gene expression rate (Rabascio et al. 2010). Non-Hodgkin Lymphoma, rheumatoid arthritis were the indications (Nieri et al. 2009). CD137 is a costimulatory molecule expressed on a variety of immune cells after activation, including NK cells. CD137 stimulation by specific IgG enhances the antilymphoma activity of anti-CD20 antibodies by enhancing ADCC (Kohrt et al. 2011). Of 153 pregnancies with known outcomes, 90 resulted in live births. Twenty-two infants were born prematurely; with one neonatal death at 6 weeks. Eleven neonates had hematologic abnormalities; none had corresponding infections. Four neonatal infections were reported (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis). Two congenital malformations were identified: clubfoot in one twin, and cardiac malformation in a singleton birth. One maternal death from pre-existing autoimmune thrombocytopenia occurred. Women should continue to be counseled to avoid pregnancy for $\leq$12 months after rituximab exposure; however, inadvertent pregnancy does occasionally occur. Practitioners are encouraged to report complete information to regulatory authorities for all pregnancies with suspected or known exposure to rituximab (Chakravarty et al. 2011). Due to ongoing bleeding, rituximab was given in the 26th week of pregnancy. The platelet count rose to over 100 $\times$ 10(9)/L after 4 weeks. The neonatal B-lymphocyte count normalized at 4 months after delivery. There were no neonatal complications of rituximab therapy (Gall et al. 2010). Passenger lymphocyte syndrome has been described by Lee et al. (2008a, b).

Siplizumab (CD2 or MEDI-507) is a humanised IgGlK monoclonal antibody that binds to human CD2 antigen. Preclinical studies demonstrated that siplizumab kills target cells by ADCC (Fanale and Younes 2007; Watanabe 2011).

Teplizumab (CD3-specific, hOKT3γ1-Ala-Ala), a humanized Fc mutated anti-CD3 monoclonal antibody induced tolerance, on the progression of type 1 diabetes in patients with recent-onset disease even 2 years after the first diagnosis (Herold et al. 2002, 2005).

Tocilizumab (TOC, RoActemra, Roche) Against receptor of IL-6 (mouse anti–-human IL-6R antibody into human IgG1-κ chain to create a human antibody with a human IL-6R binding site IL-6R α-chain or CD126; β-chain or CD130) At a low concentration of 1 microg/mL, tocilizumab (anti-human IL-6 receptor monoclonal antibody) inhibited the IL-6-induced matrix-metallo-proteinase (MMP) secretion which was shown to be stimulated in preterm premature rupture of membranes (PPRM) (Sato et al. 1993; Mano et al. 2009; Malottki et al. 2011; Pham et al. 2010). Clinical phase 3 trial for the treatment of rheumatoid arthritis has been approved. Inherited autoinflammatory syndrome can be sometimes treated with anakinra and tocilizumab (Goldfinger 2009). At present reports on abatacept, tocilizumab or

anakinra are inconclusive therefore throughout pregnancy cannot be recommended (Østensen and Förger 2011).

Normal pregnancy is characterised by elevated Th2 activity and anti-inflammatory cytokines during the first trimester, followed by increased Th1 activity and pro-inflammatory factors near term (Challis et al. 2009). In contrast, preeclampsia (PE) is marked by an increase in proinflammatory tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) cytokines as well as a decrease in the anti-inflammatory cytokines IL-4 and IL-10. In cases of restricted fetal growth, TNF-α is also elevated when compared with normal pregnancy (Dávila et al. 2011). Women living at 3,100 versus 1,600 m in Colorado had higher proinflammatory (IL-6, TNF-α) relative to anti-inflammatory (IL-10) cytokines during the second and third trimesters (Coussons-Read et al. 2002). Multigenerational Andean versus shorter duration European high-altitude residents were found to be protected from altitude-associated fetal growth restriction. Higher IL-1β might play a role in protection from altitude-associated reductions in fetal growth (Coussons-Read et al. 2002; Dávila et al. 2011). Tocilizumab treatment increased serum levels of IL-6 and soluble IL-6R (sIL-6R; Nishimoto et al. 2008). In combination with other drugs adult onset of Still's disease can be improved using monoclonal antibodies (Efthimiou and Georgy 2006).

Tositumomab anti-CD20 IgG, B-cell lymphoma (Armstrong and Eck 2003; Nieri et al. 2009).

Trastuzumab (Herceptin) Humanized, IgG1κ, ErbB2, anti-HER2. Induction of CDC or ADCC on an FcReceptor γ-binding mechanism. Human anhydramnion and oligohydramnion will develop because of the caused fetal kidney insufficiency (Watson 2005; Robinson et al. 2007; Katsumi et al. 2008; Matsumoto et al. 2009). This decrease in amniotic fluid seems to be reversible with the discontinuation of trastuzumab (Sukumvanich 2011). Transfer using AAV-recombinant in mice does not induce anti-idiotypes (Wang et al. 2010a, b).

The mechanism of toxicity to the fetal kidneys is proposed to be associated with the different structure of EGFR in the fetal renal-tubule epithelial cells (heterodimer of EGFR and ErbB2 in fetus vs. homodimer of EGFR in adults). Thus, trastuzumab will have a damaging effect on the fetal renal function, but it does not affect the kidneys of the adult (Robinson et al. 2007).

Anti-Trastuzumab (Ladjemi et al. 2011): Anti-trastuzumab anti-Id scFv69, used as a therapeutic or prophylactic vaccine, protects mice from developing HER2-positive mammary tumors by inducing both anti-HER2 Ab1′ antibody production and an anti-HER2 Th2-dependent immune response. These results suggest that scFv69 could be used as an anti-Id-based vaccine for adjuvant therapy of patients with HER2-positive tumors to reverse immunological tolerance to HER2. Calmodulin inhibitors rescue Trastuzumab sensitivity of breast tumours (Kulkarni et al. 2010). The majority of these patients were able to tolerate therapy; however, oligohydramnios or anhydramnios occurred in 5 out of the 7 patients. This decrease in amniotic fluid seems to be reversible with the discontinuation of trastuzumab (Sukumvanich 2011).

Tremelimumab (CP-675,206; Pfizer); CTLA-4 (CD152) T cells; T_{REG} cells; colon and prostatic cancer; (Houot et al. 2011).

TriAb 11D10 (TriAb) Breast cancer (Reece et al. 2000, 2001, 2003).

TriGerm (disialoganglioside GD2) Melanoma (Foon et al. 2000). Tositumomab (Iodine labelled), Murine CD20, CDC, ADCC, radio-cytotoxicity non-Hodgkin-Lymphoma (Nieri et al. 2009)

Veltuzumab is a humanized anti-CD20 antibody with structure-function differences from chimeric rituximab (Watanabe 2011).

Visilizumab (CD3-specific) for the management of both Crohn's disease (CD) and ulcerative colitis (UC). Biologics under evaluation or approved for UC that are discussed include monoclonal antibodies to tumor necrosis factor ([TNF] infliximab), inhibitors of adhesion molecules (MLN02 and alicaforsen), anti-CD3 antibodies (visilizumab), and anti-interleukin (IL)-2 receptor antibodies (daclizumab). Biologics under evaluation or approved for CD that are reviewed include three monoclonal antibodies to TNF (infliximab, adalimumab, and certolizumab pegol), monoclonal antibodies against IL-12, interferon-γ, and IL-6 receptors, inhibitors of adhesion molecules (natalizumab, alicaforsen), and growth factors. Only the chimeric monoclonal anti-TNF antibody infliximab is currently available worldwide (D'Haens and Daperno 2006).

^{90}Yttrium-ibritumomab tiuxetan and ^{131}Iodine-rituximab are anti-CD20 monoclonal antibodies combined with radioactive materials for diagnostic and/or therapeutic applications (Watanabe 2011).

Zalutumumab anti-EGFR MAB able to facilitate complement lysis of cancer cells (Klausz et al. 2011). Reviewed recently (Quatrale et al. 2011).

9.4.2.2 Grouping of Target Molecules (or Epitopes) of Therapeutic MABs

CD2	Expressed by antigen presenting myeloid cells (APC) (Magnani et al. 2011).
CD3	T-cell receptor (TCR)–CD3 complex resulting in the cells becoming 'blind' to antigen, a process that is also known as antigenic modulation (Chatenoud and Bluestone 2007).
CD20	Over 90% of malignant B-lymphoma express it (Miura et al. 2011)
CD22	B-cell antigen receptor (BCR), cell surface CD22, CD40 and serum B-lymphocyte stimulator are predominant receptors/ligands necessary for mature B-cell survival in the periphery (Smith et al. 2010).
CD25	T_{REG} cell membrane antigen
CD30	CD30 is selectively overexpressed in the malignant cell population of Hodgkin's lymphoma (Ansell et al. 2007).
CD33	Membrane antigen of acute myeloid leukemia cells (De Propris et al. 2011)
CD34	(Tanaka et al. 2001)
CD40	B-cell TNF-receptor (Chatenoud and Bluestone 2007; Houot et al. 2011)
CD52	Antigen present in acute myeloid leukemia cells (Saito et al. 2011).
CD80	Membrane antigen of follicular B-cell lymphoma (Watanabe 2011)
CD86	(B7.1 – CD80 and B7.2 – CD86) natural ligands of CD28/CTLA-4 system (Salek-Ardakani et al. 2009)
CD128	IL6-receptor alpha chain (Sato et al. 1993).
CD152	CTLA-4 negative regulator of T cell activation (Kaufman et al. 1999).

TRAIL	DR5/TNF related receptor (Nieri et al. 2009).
VGF-A	Vascular growth factor A in cells of colorectal cc (Pentsuk and van der Laan 2009)
VGFR	Vascular growth factor receptor, angiogenesis (Krupitskaya and Wakelee 2009)
EGFR/HER	Epidermal growth factor receptor/HER (Quatrale et al. 2011).
IGFR	Insulin-like growth factor (Quatrale et al. 2011).
IL6	Interleukin 6 (Naugler et al. 2007; Naugler and Karin 2008; Voorhees et al. 2009; Reinartz et al. 2009).
PD-1	Programmed death protein 1 (Houot et al. 2011).
Complement factor 5	Thomas et al. (1996)
Breast cancer protein	Reece et al. (2000, 2001, 2003)
IgE	Immunoglobulin E, hypersensitivity (Corren et al. 2009).
anti-idiotypes	Carrier of the mimicry of epitopes (Ab2) of antigens (Köhler 1978).
RSV	Respiratory syncytial virus (Nieri et al. 2009).

Cytotoxic T lymphocyte antigen-4 (CTLA-4) and Programmed cell death 1 (PD-1) are members of the known T_{REG}-associated molecules. Blocking PD-1 abrogate the protective effect of T_{REG}, resulting in a higher median abortion rate in comparison with the T_{REG} / isotype-treated control while CTLA-4 blockage did not interfere with the protective effect of T_{REG}. PD-1 as an important mediator in T_{REG}-induced fetal protection in the CBA/ J · DBA/ 2J murine model (Wafula et al. 2009).

CTLA-4 was shown to interact with CD80 and CD86 resulting in termination of immune response (Alegre et al. 2001). Mice genetically deficient in CTLA-4 expression develop a lymphoproliferative disease which terminates in death by 3–5 weeks of age (Tivol et al. 1995; Waterhouse et al. 1995). The CD28 possesses also role in the regulation of T-cells (Sansom and Walker 2006). Blockade of the interactions between CD28 and their ligands, CD80 and CD86, has been shown to induce antigen-specific peripheral tolerance in organ transplantation. This knowledge has been successfully used in animal models to prevent allograft rejection by blocking CD86 and/or CD80, thereby leading to long-term graft survival.

Cytokines favoring the maintenance of fetal survival mainly belong to the Th2-type (e.g. IL-4, IL-10, TGF-β), whereas pregnancy failure is associated with the Th1-type cytokines (e.g. IFN-γ, TNF-α) at the materno-fetal interface and/or the absence of Th2-type cytokines. The combined use of anti-CD80 and anti-CD86 mAbs in mice was effective in inducing maternal tolerance to the allogeneic fetus.

Blockade *in vivo* of CD80 and CD86 costimulation could prevent abortions by shifting cytokines from Th1 predominance to Th2 bias and expanding peripheral $CD4^+CD25^+$ regulatory T cells (Jin et al. 2005). Breakdown of immunologic self tolerance maintained by activated T cells expressing IL-2 receptors (CD-25) results

in the development of autoimmune diseases (Sakaguchi et al. 1995; Sakaguchi 2004), which can be mitigated using anti-CD25 monoclonals. Suppressive $CD4^{+}CD25$ T_{REG} cells are elevated also during pregnancy (Somerset et al. 2004).

Intergins: progressive multifocal leukoencephalopathy was observed (PML) probably of polyomavirus etiology after natalizumab (anti-integrin-α4) therapy of Crohn's disease (Edula and Picco 2009).

9.4.2.3 Adult Complications of the Therapy with Tnfα Inhibitors

TNFalpha blockers were shown to induce autoimmunity on ANA and anti-dsDNA antibodies in RA and SPA patients. Autoimmunity was induced more frequently with infliximab than etanercept and to a lesser degree to adalimumab therapy but, more importantly, this emergent autoimmunity was exceptionally associated to clinical manifestations of lupus (Bacquet-Deschryver et al. 2008). The effect of infliximab, etanercept or adalimumab on spermatogenesis has been studied in 26 patients with spondylarthritis (Villiger et al. 2010). Sperm abnormalities were found in healthy controls. Patients on anti-TNF therapy showed significantly better sperm motility and vitality than untreated patients (Østensen and Förger 2011).

9.4.3 Virus-Specific Therapeutic Monoclonal Antibodies

Antibody products licensed for prevention or treatment of viral diseases include non-immune human immunoglobulin for use against hepatitis A and measles, virusspecific polyclonal human immunoglobulin against cytomegalovirus, hepatitis B, rabies, respiratory syncytial virus (RSV), vaccinia, and varicella-zoster, and the humanized monoclonal antibody palivizumab, fonolizumab and motavizumab (Groothuis et al. 2011).

Polyclonal immunoglobulin has also been used with various success for diseases caused by other human viruses including parvovirus B19 (PV B19), Lassa virus, West Nile virus, some enteroviruses, herpes simplex virus, Crimean-Congo haemorrhagic fever virus (CCHFV), Junin virus, Severe Acute Respiratory Syndrome-Associated coronavirus (SARS CoV) and Human Immunodeficiency Virus (HIV). Serum polyclonal antibody preparations have been clinically effective in many cases, problems related to toxicity including a risk for allergic reactions, lot to lot variation and uncertain dosing have limited their use (Casadevall 1999, 2006). The use of rabies and tick-borne encephalitis virus-specific hyperimmune gamma globulins are used in several countries immediately following virus exposure (animal injuries or tick bites). Cytomegalovirus-specific hyperimmune gamma globulin is used in the transplantation surgery (Schmitz and Essuman 1986) before the era of gancyclovir preventive therapy.

SARS CoV surface glycoprotein, also called spike glycoprotein, (S protein or S glycoprotein) mediates viral entry into the host cell and has two functional

domains S1 and S2. The S1 domain is involved in the binding of the cellular receptor ACE2 whereas the S2 domain facilitates the fusion between viral and host cell membranes. Infections by many viruses, including coronaviruses, elicit potent neutralizing antibodies (nAbs) that can affect the course of infection and help clear the virus; they can also protect an uninfected host exposed to the virus. An improved method for Epstein-Barr Virus (EBV) transformation of human B cells has been developed based on CpG oligonucleotides that increases the B cell immortalization efficiency from 1–2% to 30–100%, and this method was used for selection of human Abs specific for SARS CoV proteins. One of the selected antibodies, which was specific for the S glycoprotein on the viral spikes, was about 500-fold more efficient in neutralization than convalescent serum.

Nipah virus (NiV) and Hendra virus (HeV) are closely related emerging paramyxoviruses that comprise the Henipavirus genus. They are Biological Safety Level-4 (BSL-4) pathogens, and are on the NIAID biodefense research agenda as zoonotic emerging category C priority pathogens that could be used as bioterror agents (Zhu et al. 2008).

9.4.4 Monoclonal Abzyme Therapy

Monoclonal antibodies of enzyme activity have been developed. These can be used in cancer therapy, but the application for the treatment of pregnant women is at present not yet approved (Kulkarni et al. 2010; Quatrale et al. 2011). Immunotherapy offers a range of potential treatment options: drug treatment, as well as the treatment of overdose, prevention of brain or cardiac toxicity and fetal protection in pregnant drug abusers. Clinical trials, cocaine and nicotine vaccines have been shown to induce antibody titers while producing few side effects (Haney and Kosten 2004). Plasmin may serve as a major driving autoantigen for some anti-cardiolipin (aCL) in anti-phospholipid syndrome (APS) patients who are positive for IgG anti-plasmin Ab. One mAb displayed the anti-cardiolipin (aCL) and the lupus anti-coagulant (LAC) activities and induced fetal loss when injected into pregnant mice (Chen et al. 2007).

9.4.5 Molecular Mimicry in the Pathogenesis of Connatal Illnesses

Molecular mimicry has been suggested to play a role in the pathogenesis of many autoimmune diseases, such as allergic encephalomyelitis, experimental myocarditis, and experimental autoimmune keratitis and uveitis Antigenic molecular mimicry is characterising anti-DNA antibodies. These are reacting with different proteins i.e. enzymes (Blank and Shoenfeld 2004). In case of schizophrenia,

the overall finding has been that, when a monozygotic twin has this serious neuromental disorder (NMD), the other identical twin has a 50% risk; whereas among dizygotic twins, the risk – when one is afflicted – is only 15%.

Neuromental disorders (NMD) might be caused indirectly by maternal transplacentally-acquired antibodies, to agents with epitope molecular mimicry with the developing nervous system, and cause alterations which will clinically manifest years later (Nahmias et al. 2006). Serological evidence of previous exposure to EBV in children with MS supports a role for EBV infection early in MS pathogenesis, as already indicated by prospective studies in adults. Higher antibody titers and T-cell responses to EBV in patients compared to healthy EBV carriers indicate possible continuous viral reactivation.

MS patients have increased $CD4^+$ and $CD8^+$ T-cell responses to EBV antigens, particularly EBNA1. There is some evidence that EBV could break immune tolerance to myelin antigens through molecular mimicry. Detection of EBV-infected B-cells in patients' brain raises the possibility that intrathecal B-cell abnormalities and T-cell-mediated immunopathology in MS are the consequence of a persistently dysregulated EBV infection. Accordingly, targeting T-cells and/or B-cells with monoclonal antibody therapies ameliorates MS. Whether EBV has a causative or pathogenic role in MS can now be addressed in relation to genetic, hormonal and other environmental influences that may affect EBV–host interactions (Salvetti et al. 2009). Functional suppression by $CD4^+CD25^+$ regulatory T cells was also found to be impaired in MS patients (Viglietta et al. 2004).

9.5 Effects of Interferon Therapy During Pregnancy

Newborns of pregnants suffering from multiple sclerosis (MS) were impaired by the disease. In case the father of the newborn was suffering from MS, no negative consequences could be documentet i.e. safe paternity characterises MS-patients. The results of mothers does not seem to have an impact on birth weight, however, MS may contribute to a reduced birth weight (Hellwig et al. 2010). The mothers suffering from MS are usually treated with long-term interferon (IFN) beta-therapy in spite of the pregnancy. The foetal exposure to subcutaneous interferon beta-1a therapy before treatment discontinuation was at least 28 days; most pregnancies (199/231; 86.1%) were exposed for $\leq$45 days. The rates of spontaneous abortion and major congenital anomalies in live births were in line with those observed in the general population (Amato et al. 2010; Sandberg-Wollheim et al. 2011). The *in vitro* susceptibility of BeWo cells was increased for *Toxoplasma gondii* following treatment with interferon gamma, interleukin 10 and transforming growth factor 1-beta (Barbosa et al. 2008), but similar consequences were not observed during pregnancy *in vivo*.

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