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ESSENTIALS Therapeutic monoclonal antibodies and related molecules are increasingly used to treat immune-mediated and inflamma- tory diseases. They interact very precisely with a soluble or cell- bound ligand to have three predominant effects: neutralization of proinflammatory cytokines or growth factors; modulation of intercellular interactions; or depletion of pathogenic cells. They deliver significantly enhanced specificity in comparison to trad- itional synthetic drugs and have delivered substantial improve- ments in clinical outcomes in many immune, inflammatory, and allergic diseases. However, there are no biomarkers to help de- cide which biological class to try first in a particular patient, hence one of the main challenges for the future is the identification of ‘stratifiers’ to guide therapy. Introduction A biological therapy is a medicinal product that is produced from a biological source, usually a living cell, in contrast to a synthetic, small molecule drug. Biological therapies include growth factors, hor- mones, and other recombinant therapeutic proteins, but this chapter will focus on therapeutic monoclonal antibodies (mAbs) and related molecules in the context of immune-mediated and inflammatory diseases (Table 2.7.1). The overriding concept underpinning these molecules is that they are ‘targeted therapies’, developed to interact very precisely with a soluble or cell-bound ligand. In this way they have significantly enhanced specificity in comparison to traditional synthetic drugs. In the 30 years since the first mAb was licensed for acute trans- plant rejection the field has expanded rapidly (see Chapter 3.8). These complex molecules are now a multibillion-dollar industry and occupy an enlarging space in the global pharmaceutical market. Growth has been catalysed by increased knowledge of dis- ease pathologies but also by advances in protein engineering and bioprocessing, which have improved the efficiency of therapeutic protein production as well as the quality of the products. The development of therapeutic antibodies and derivatives In the 1970s Kohler and Milstein developed technology that enabled the isolation and immortalization of B-cell clones (hybridomas) producing a particular type of antibody. The product of each clone was a mAb of unique and defined

specificity, which raised hopes of modern-day ‘magic bullets’ to target cancers and other diseases. The first licensed mAb was OKT3, a murine mAb against the antigen CD3 on T cells. This reversed steroid-refractory transplant rejection with significant success, despite a cytokine release syndrome precipitated by T-cell activation. A further limitation was immunogenicity, a consequence of the recipient’s immune system viewing the murine mAb as a foreign protein. The resulting immune (antiglobulin) response neutralized the mAb and accelerated its clearance, frustrating attempts to retreat patients and occasionally causing hypersensitivity reactions. Concurrent advances in recombinant DNA technology, how- ever, enabled the cloning, manipulation, and recombination of antibody genes from hybridomas (Fig. 2.7.1). The next generation of therapeutic mAbs were chimeric, whereby the murine variable (V) region, responsible for target-binding, remained intact but was linked to a human constant (C) region, with an incremental reduc- tion in ‘foreignness’. In a further iteration, the complementarity- determining regions (CDRs) of the murine mAb (the V-region elements that determined specificity) were left intact but embedded in a human framework, providing ‘humanized’ mAbs. Ultimately, ‘fully human’ mAbs were produced, either from transgenic animals whose genomes had been manipulated to produce human anti- bodies upon immunization; or by in vitro techniques such as phage display technology. As well as reducing potential immunogenicity these techniques enabled the engineering of antibody C-regions, to enhance or reduce effector function, and thereby the fate of the mAb target. Antibody fragments were also generated, both intact Fab fragments and smaller elements that retained target-binding capacity; other technologies enabled the generation of antibody-drug conjugates and bispecific antibodies of dual specificity. Receptor-fusion proteins resemble 2.7 Biological therapies for immune, inflammatory, and allergic diseases John D. Isaacs and Nishanthi Thalayasingam

2.7 Biological therapies for immune, inflammatory, and allergic diseases 101 Table 2.7.1 Currently licensed biological therapies for immune, inflammatory, and allergic diseases Drug name Target Structure Licensed indication(s) Route of administration Notes Abatacept CD80/CD86 Fusion protein of CTLA4 EC domain and human IgG1 Fc RA, JIA SC (RA); IV (RA, JIA) Fc is modified to prevent cytotoxicity Adalimumab TNF Fully human mAb RA; JIA; CD; UC; AS; PsA; Ps; Hidradenitis suppurativa, uveitis SC Biosimilar available Alemtuzumab CD52 Humanized mAb MS IV Also used extensively for lymphoma/ leukaemia and conditioning of solid organ and bone marrow transplant recipients Anakinra IL-1 Recombinant human IL-1 receptor antagonist RA; CAPS; Still’s disease SC Recombinant form of naturally occurring IL-1 receptor antagonist Atacicept BLyS, APRIL Fusion protein of TACI EC domain and human IgG1 Fc SLE SC In development Belimumab Blys Fully human mAb SLE IV Benralizumab IL-5 receptor Humanized mAb Eosinophilic asthma SC Brodalumab IL-17RA Fully human mAb Ps SC Canakinumab IL-1β Fully human mAb Gout; JIA (systemic); CAPS; Still’s disease SC Certolizumab Pegol TNF Humanized mAb Fab' fragment linked to PEG RA; AS; PsA; Ps SC Denosumab RANKL Fully human mAb Osteoporosis SC Cases of osteonecrosis of the jaw and atypical femoral fractures have been reported Etanercept TNF Lymphotoxin Fusion protein of human p75 TNF receptor EC domain and human IgG1 Fc RA; AS; JIA; PsA; Ps SC Ineffective in CD Biosimilar available Etrolizumab β7 integrin Humanized mAb IBD SC In development Golimumab TNF Fully human mAb RA; AS; PsA; UC SC Guselkumab IL-23 (p19 subunit) Fully human mAb Ps SC Infliximab TNF Chimeric mAb RA; CD; UC; PsA; AS, Ps IV Biosimilar available Ixekizumab IL-17A (both IL-17A and IL-17A/F) Humanized mAb PsA; Ps SC Can exacerbate IBD Mepolizumab IL-5 Humanized mAb Eosinophilic asthma SC Natalizumab α4 integrin Humanized mAb MS IV Increased susceptibility to PML Ocrelizumab CD20 Humanized mAb MS IV Omalizumab IgE Humanized Mab Allergic asthma; chronic spontaneous urticaria SC Dose determined by serum IgE and body weight

in allergic asthma Reslizumab IL-5 Humanized mAb Eosinophilic asthma IV Rituximab CD20 Chimeric mAb RA; GPA; MPA; NHL; CLL IV Dosing regimen differs between rheumatological and haematological indications Biosimilar available Sarilumab IL-6 receptor Fully human mAb RA SC Secukinumab IL-17A Fully human mAb Ps, PsA, AS SC Can exacerbate IBD Tildrakizumab IL-23 (p19 subunit) Humanized mAb Ps SC Tocilizumab IL-6 receptor Humanized mAb RA; JIA; GCA IV (RA, JIA); SC (RA) Ustekinumab IL-12 & IL-23 (p40 subunit) Fully human mAb Ps, PsA; CD SC Inhibits Th1 and Th17 pathways Vedolizumab α4β7 integrin Humanized mAb CD, UC IV Abbreviations: CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte associated protein 4; EC, extracellular; Ig, immunoglobulin; Fc, fragment crystallisable; RA, rheumatoid arthritis; JIA juvenile idiopathic arthritis; SC, sub-cutaneous; IV, intravenous; TNF, tumour necrosis factor; mAb, monoclonal antibody; CD, Crohn's Disease; UC, ulcerative colitis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; Ps, psoriasis; MS, multiple sclerosis; IL, interleukin; CAPS, cryopyrin-associated periodic syndrome; BLyS, B-lymphocyte stimulator; APRIL, a proliferation-inducing ligand; TACI, transmembrane activator and CAML interactor; SLE, systemic lupus erythematosus; RA, receptor A; Fab, fragment antigen binding; PEG, polyethylene glycol; RANKL, receptor activator of nuclear factor kappa-B ligand; IBD, inflammatory bowel disease; PML, progressive multifocal leukoencephalopathy; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; GCA, giant cell arteritis; Th, T helper cell.

102 section 2 Background to medicine mAbs but comprise the extracellular domain of a cell surface receptor fused to an immunoglobulin (Ig) Fc to form a soluble molecule that is specific for the receptor's ligand (Fig. 2.7.2). For further discussion see account by H Waldmann and G Winter in Chapter 3.8. Classification The structure of a therapeutic mAb can be discerned by its no- menclature and is comprised of: prefix, substem A, substem B, and suffix. The prefix is unique to the drug and the suffix, -mab, indicates that it is a mAb. Substem B provides the species upon which the Ig sequence is based: u for human, o for mouse, xi for chimeric, and zu for humanized. Substem A indicates the class of drug (e.g. -l(i)- for immunomodulatory, k(i) for interleukin and t(u) for tumour). Some examples are provided in Table 2.7.2. Targets for biological therapies in immune-mediated inflammatory diseases In immune-mediated inflammatory diseases, biological therapies act in three predominant ways: to neutralize proinflammatory cyto- kines or growth factors; to modulate intercellular interactions; or to deplete pathogenic cells (see Fig. 2.7.3 and Table 2.7.1). Cytokine and growth factor targets Tumour necrosis factor (TNF) TNF is a pivotal cytokine mediator in a variety of immune-mediated inflammatory diseases. It exists in soluble and transmembrane forms, and binds to type 1 and type 2 receptors to mediate a var- iety of proinflammatory and cell survival effects. TNF blockade was the first of the modern-day biological therapy paradigms and has been licensed for adults and children with a variety of rheum- atological conditions (rheumatoid arthritis, ankylosing spondyl- itis, psoriatic arthritis, juvenile idiopathic arthritis), as well as for psoriasis, Crohn's disease, ulcerative colitis, uveitis and hidradenitis suppurativa (Table 2.7.1). There are five anti-TNF drugs currently licensed. Two are fully human mAbs, one is a chimeric mAb, one (certolizumab) is a PEGylated Fab' fragment and the last is a sol- uble receptor. The latter (etanercept) also binds lymphotoxin α3 but there is nothing to suggest this is relevant to its efficacy or toxicity. Certolizumab is the only anti-TNF manufactured in E. coli, which should increase yields over mammalian cell culture. The PEG moiety increases the half-life by reducing renal clearance and proteolysis. TNF blockade was licensed for rheumatoid arthritis at the start of the 21st century and was revolutionary. Patients who had been re- fractory

to all treatment modalities suddenly experienced previously unimagined symptomatic improvements in joint pain and stiffness, and fatigue. Furthermore, TNF blockade prevented the relentless joint damage seen with more traditional therapies. Consequently, Heavy chain Light chain CDRs VARIABLE REGION CONSTANT REGION (a) (b) MURINE CHIMERIC -XIMAB HUMANISED -ZUMAB 'FULLY HUMAN' -MUMAB Fig. 2.7.1 The different types of therapeutic antibody. (a) Basic antibody structure. (b) Basic structure of a murine, chimeric, humanized, and human monoclonal antibody. Red indicates murine sequence and black indicates human sequence. CDR, complementarity-determining region. Reproduced from: Isaacs JD. Antibody engineering to develop new antirheumatic therapies. Arthritis Res Ther 2009, 11, 225. disulphide bonds VH VL CH1 CL (b) VH VL CH1 CL VH VL CH1 CL CH2 CH2 CH3 CH3 Hinge (a) Fc (c) CH2 CH2 CH3 CH3 receptor fragment receptor fragment Fig. 2.7.2 The domain structures of an antibody molecule and derivatives. (a) An antibody molecule. (b) A fragment antigen-binding (Fab) fragment. (c) A receptor-immunoglobulin fusion protein. CH, heavy chain constant domain; CL, light chain constant domain; Fc, fragment crystallizable; VH, heavy chain variable domain; VL, light chain variable domain. NB: A Fab' fragment is a Fab fragment plus the hinge region. Reproduced from: Isaacs JD. Antibody engineering to develop new antirheumatic therapies. Arthritis Res Ther 2009, 11, 225.

 patients experienced less disability than previous generations with retained employment prospects and reduced need for joint surgery. Registry data demonstrated a slightly enhanced risk of serious in- fection (about 20% higher than with synthetic antirheumatic drugs such as methotrexate) but no enhanced risk of malignancy. An un- expected complication was the emergence of tuberculosis (TB), often disseminated and with unusual histology. Because of their targeted nature biological therapies have provided unexpected in- sights into pathophysiology. In the case of TB, we learnt that TNF was essential for the maintenance of granulomas, which in turn con- trolled latency in individuals with prior exposure. The dissolution of granulomas with TNF blockade thereby released TB bacilli into the bloodstream with extrapulmonary reactivation. Patients prescribed TNF blockade are now routinely screened for prior TB exposure and treated with appropriate prophylaxis where indicated. The soluble receptor etanercept is less likely to reactivate TB. The precise reason is unclear but may reflect a reduced capacity to disrupt granulomata due to an incapacity to perform so-called 'inside-out' signalling upon binding cell surface TNF. TNF blockade is also associated with an enhanced susceptibility to opportunistic intracellular pathogens such as listeria, salmonella, and some fungi. The effects of TNF blockade were similarly impressive in patients with severe Crohn's disease, particularly those with fistulae and peri- anal disease in which healing was rapid and complete. When used in the first two years of disease, around 50% of patients achieve remis- sion and even mucosal healing. Perhaps with parallels to TB reactiva- tion, etanercept is not effective in this granulomatous disease of the gastrointestinal (GI) tract. TNF blockade is also effective in ulcera- tive colitis. Psoriasis provided a further successful disease target, at a time when systemic treatments were relatively limited. Infliximab provided 75% improvement in the Psoriasis Area and Severity Index (PASI) in more than 80% of patients, and 90% improvements in 50– 60%. These drugs were also effective in psoriatic arthritis and an- kylosing spondylitis, for which therapeutic options were even more limited than for rheumatoid arthritis. In both diseases they provide significant improvement in disease activity, including spinal inflam- mation and function. In contrast, TNF blockade was not successful in other indica- tions characterized by TNF excess, perhaps illustrating homeostatic functions of TNF. These included multiple sclerosis and congestive

heart failure, in which trials were stopped prematurely for disease worsening. Uncommon and unexpected adverse effects of TNF blockade include neutropenia and vasculitis and, paradoxically, psoriasis can be triggered in some patients. Drug-induced lupus can also occur, including renal and cerebral manifestations. IL-6 IL-6 is a key local and systemic inflammatory mediator. Its receptor exists in membrane-bound and soluble forms. After binding IL-6, the soluble receptor pairs with its signalling component, gp130, on any cells that express it. Tocilizumab binds both forms of the IL-6 receptor, effectively preventing IL-6 signalling. The protean effects of IL-6 include: activation of B and T cells, and macrophages; the differentiation of macrophages into osteoclasts; synovial fibroblast proliferation and synovial neovascularization; production of plate- lets from megakaryocytes; production of acute phase reactants and hepcidin from the liver; and systemic effects such as fever and Table 2.7.2 Mab nomenclature Prefix Substem A Substem B Suffix Infliximab Inf li Xi Mab Tocilizumab Toci li Zu Mab Canakinumab Cana ki nu Mab Rituximab Ri tu xi Mab (a) (b) (c) Fig. 2.7.3 Potential mechanisms of action of immunomodulatory mAbs and receptor-immunoglobulin fusion proteins. (a) Neutralization of soluble mediators. (b) Cell lysis. (c) Inhibition of intercellular or cell: endothelial interactions.

104 section 2 Background to medicine fatigue. Il-6 levels are elevated in rheumatoid arthritis, particularly within the joint, and administration of tocilizumab provides re- ductions in disease activity similar to TNF blockade. In line with hepatic effects of IL-6 there is a robust normalization of the acute phase response and, in patients with anaemia of chronic disease, a rise in haemoglobin as hepcidin levels fall. Elevated platelet counts also fall. Dyslipidaemia may occur in patients receiving tocilizumab with elevations in HDL, LDL, and triglycerides, usually without a rise in atherogenic index. Nonetheless lipid rises should be treated according to relevant guidelines. Diverticular perforations have oc- curred in patients receiving tocilizumab, which should therefore be used with caution where there is a history of intestinal ulceration or diverticulitis. The aetiology is unclear but could reflect an important homeostatic role of IL-6. Reversible neutropenia and transaminase elevation are also common. In other respects, the efficacy and ad- verse event profile of IL-6 blockade resemble those of TNF blockade. In particular there is a slightly enhanced risk of serious infections. IL-1 IL-1α and IL-1β are proinflammatory and bind the IL-1 receptor (IL-1R). The naturally occurring IL-1 receptor antagonist (IL-1Ra) competes with IL-1α and β for binding to IL-1R. IL-1 inhibition can be achieved with anakinra (recombinant IL-1ra), or with canakinumab (anti-IL-1 mAb). Anakinra effectively blocks IL-1α and IL-1β but its short half-life requires daily dosing. It is licensed for rheuma- toid arthritis and for the autoinflammatory cryopyrin-associated periodic syndromes (CAPS), in which the activated inflammasome results in increased secretion of IL-1β. These include neonatal- onset multisystem inflammatory disease (NOMID), chronic in- fantile neurological, cutaneous, articular syndrome (CINCA), Muckle–Wells syndrome, and familial cold autoinflammatory syndrome (FCAS). In rheumatoid arthritis, despite elevated IL-1 levels in plasma and synovial fluid, the efficacy of anakinra is less than that of the other biological drugs. Canakinumab is an anti-IL- 1β human mAb, licensed for the treatment of CAPS, systemic ju- venile idiopathic arthritis (JIA), and gouty arthritis. In gout, urate crystals are ingested by neutrophils and monocytes, activating the inflammasome with the release of IL-1β. IL-17 IL-17A is the signature cytokine of Th17 T cells which, in health, protect against bacterial and fungal infections, particularly candid- iasis. Other members of this cytokine family include IL-17F, IL-17C, and IL-17A/F. The various family members bind receptors that share the subunit IL-17RA. Th17 T cells are also associated with a number of autoimmune diseases including rheumatoid arthritis, psoriasis, inflammatory bowel disease, and ankylosing spondylitis. The func- tions of IL-17 overlap with those

of TNF and IL-6, while also stimu- lating the production of additional proinflammatory cytokines and chemokines. Akin to IL-6, IL-17 promotes osteoclastogenesis and angiogenesis. Secukinumab is a fully human anti-IL-17A antibody. The drug penetrates the skin and reduces local inflammation asso- ciated with psoriasis. In a head-to-head study its efficacy exceeded that of etanercept, with 54% of patients achieving PASI 90 and 24% PASI 100 after 12 weeks. It is also an effective treatment for psoriatic arthritis and ankylosing spondylitis. While IL-17A is abundantly present in the gut mucosa in inflammatory bowel disease (IBD), secukinumab was ineffective in Crohn's disease and associated with infectious complications. Furthermore, IBD exacerbations were re- ported in trials of secukinumab for other indications. Blockade of IL-17A is associated with infections, including mucosal and, occa- sionally, systemic candidiasis. Brodalumab targets IL-17- RA, thereby antagonizing the different IL-17 family members; it is licensed for use in moderate to severe plaque psoriasis. B-lymphocyte stimulator B-lymphocyte stimulator (BLyS), also known as B-cell activating factor, is a B-cell survival factor and a member of the TNF super- family. Levels are elevated in certain autoimmune diseases such as systemic lupus erythematosus (SLE), where there is an association with disease activity. Inhibition of BLyS leads to impaired B-cell survival and reduced differentiation of B cells into plasma cells. Belimumab is a fully human anti-BLys mAb. It is the only biological drug to be approved in the treatment of SLE, with a licence for pa- tients with active, autoantibody positive disease. Administration of belimumab is associated with reductions in IgG levels, including autoantibodies; longer-term administration is associated with a fall in circulating B cells. Bacterial infections are more common in pa- tients receiving belimumab. Atacicept (TACI-Ig) is a fusion protein comprising the ligand binding portion of the BLyS receptor TACI (transmembrane activator and CAML interactor) and a human IgG1 Fc. As well as binding BLyS, TACI also binds a proliferation-inducing ligand (APRIL), which is an additional B-cell growth factor. Hence atacicept has a broader anti-B-cell profile than belimumab, and is currently under investigation in SLE. IL-23 Th17 differentiation is partly controlled by IL-23, produced by den- dritic cells and by Th17 cells themselves. IL-23 comprises two sub- units, p40 shared with IL-12 (important in the differentiation of Th1 cells), and p19. Ustekinumab is a fully human anti-p40 mAb that blocks the actions of both IL-23 and IL-12. It is effective for treating severe plaque psoriasis and psoriatic arthritis although showed inferiority to secukinumab in a head-to-head trial in psor- iasis. It is also licensed for use in Crohn's disease, in contrast to IL-17 blockade. Guselkumab, which blocks IL-23 p19 (and therefore spe- cific for IL-23 vs. IL-12) is in development for similar indications, and is licensed for use in moderate to severe plaque psoriasis. Modulation of intercellular interactions A second strategy for biological therapies involves the inhibition of cell interactions, which can prevent activation or migration. Costimulation blockade T cells require two critical signals for their activation. The first is the recognition, by the T-cell receptor, of their cognate antigen (a complex of major histocompatibility complex (MHC) molecule and peptide) on an antigen presenting cell (APC). The second is the rec- ognition of CD80 and CD86 on the APC by CD28, which provides an essential costimulatory signal. Following activation the T-cell upregulates CTLA4, which displaces CD28 from CD80 and CD86 due to its higher affinity. CTLA4 imparts a negative signal to the T-cell, thereby acting as a 'brake' to activation, returning the T-cell to its resting state. Abatacept, or CTLA4-Ig, is a fusion protein of the extracellular domain of CTLA4 and a modified Fc region of human IgG1 (Fig. 2.7.4). This molecule competes with CD28 for binding to

 CD80 and CD86, thereby blocking costimulation and inhibiting the activation of naïve T cells. The Fc modification is designed to pre- vent abatacept from killing APCs to which it binds. It is an effective agent in

patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriatic arthritis. It can be administered by monthly infusion or weekly subcutaneous injection. Adhesion molecule blockade Natalizumab is a humanized anti-α4-integrin mAb which blocks the interaction of α4β1 integrin with its receptor vascular cell ad- hesion molecule-1 (VCAM-1) and α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MadCAM-1). This prevents the transendothelial migration of integrin-expressing leucocytes into inflamed tissues. In multiple sclerosis VCAM-1 is upregulated on CNS endothelium and possibly glial cells and natalizumab is an effective therapy, administered by four-weekly infusion. However, its use is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), the opportunistic infection associated with John Cunningham (JC) virus. Patients receiving natalizumab for multiple sclerosis must be fully informed of this risk and carry a patient alert card. While also effective in Crohn's disease, by inhibiting leucocyte adhesion to MadCAM-1 on gut endothelial cells, natalizumab is rarely used for this indication as a result of the PML risk. In contrast, vedolizumab is a humanized anti-α4β7 mAb. α4β7 integrin is expressed preferentially on a specific subset of gut- homing memory T cells that cause inflammation in inflammatory bowel disease. Vedolizumab therefore blocks leucocyte trafficking to the gut, with a licence for both Crohn's disease and ulcera- tive colitis. Etrolizumab is an anti-β7 humanized mAb that binds both α4β7 and αEβ7 integrins. The latter is selectively expressed on gut mucosal intraepithelial T cells, where it binds E-cadherin. Hence etrolizumab can prevent T cells trafficking to the gut but may also block their retention. It is currently under investigation in inflammatory bowel disease, having demonstrated efficacy in a phase 2 trial in ulcerative colitis. Depletion of pathogenic cells Alemtuzumab, which targets CD52 on lymphocytes, monocytes, macrophages, and NK cells, was the first humanized therapeutic mAb. It is unusual in having its origins in a rat rather than a mouse mAb. It is potently cytotoxic and, while first developed to treat leu- kaemia and lymphoma, it was subsequently studied in a range of autoimmune diseases. It is licensed for relapsing remitting mul- tiple sclerosis, administered as two short, annual treatment cycles. Its use is paradoxically associated with the development of sec- ondary autoimmunity. The most common manifestation is thy- roid autoimmunity, but more serious complications have included thrombocytopenic purpura, antiglomerular basement membrane disease, and other haematological cytopenias. Administration of alemtuzumab is also associated with significant infusion reactions, which can be reduced with appropriate premedication that includes a glucocorticoid. Oral prophylaxis for herpes virus infections is also recommended for at least one month after each treatment cycle. Rituximab is a chimeric human IgG1 anti-CD20 mAb, originally developed for the treatment of B-cell malignancies but subsequently established as an effective treatment for rheumatoid arthritis and certain types of vasculitis. It is potently cytotoxic, probably a conse- quence of efficient antibody-dependent cellular cytotoxicity, comple- ment-mediated cytotoxicity, and apoptosis induction. In rheumatoid arthritis it is administered as two intravenous infusions spaced two weeks apart, again with prophylaxis against infusion reactions. CD20 is expressed on all B cells but not on haematopoietic stem cells, pro-B cells, or plasma cells. Consequently, after initial depletion B cells reconstitute and there is minimal loss of humoral immunity due to survival of plasma cells. Reconstitution occurs typically after 6 months, but with differential rates in distinct B-cell subsets. Retreatment for rheumatoid arthritis is usually administered when MHC TCR CD28 CD80/86 Antigen presenting cell T cell Signal 1 Signal 2 (a) CD80/86 Antigen presenting cell T cell Signal 1 (b) CTLA4 MHC TCR CD28 MHC CD80/86 Antigen presenting cell TCR T cell Signal 1 (c) CD28 CTLA4-Ig Fig. 2.7.4 The structure and mode of action of abatacept. (a) T cells require two signals for full activation. Signal 2 (coactivation) derives from the interaction of CD28 with B7.1 and B7.2. (b) CTLA4 is upregulated following T-cell activation and

competes with CD28 due to its higher affinity, de-activating the T-cell. (c) Abatacept (CTLA4-Ig) is a fusion protein of the extracellular domain of CTLA4 and an IgG Fc.

106 section 2 Background to medicine symptoms start to recur but at least 6 months after the initial course. There is no recommended upper limit to the number of rituximab courses that can be administered but repeated courses are associ- ated with secondary hypogammaglobulinaemia, most commonly IgM but occasionally IgG. The latter may be associated with an en- hanced infection risk and the risk:benefit ratio of continued treat- ment should be considered before each course of therapy. PML cases have also been reported in patients who have received rituximab but most commonly in patients with leukaemia or lymphoma who have received additional immune suppression. Nonetheless all patients should be counselled about this risk and receive a patient alert card. Rituximab is also licensed for use in granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris. Immunogenicity The development of chimeric, humanized, and fully human mAbs was expected to reduce immunogenicity associated with murine components of antibody molecules. While this has largely been the case, immunogenicity cannot be eliminated altogether. MAb CDRs are intrinsically immunogenic, being created by gene recombination events and somatic mutations. There are also Ig allotypes which vary between individuals. Antidrug antibodies (ADAs) can be difficult to measure, hence their importance and extent is yet to be fully es- tablished. Nonetheless they can undoubtedly interfere with efficacy by neutralizing an mAb's binding site or accelerating its clearance. Clinically this is most likely to manifest as secondary nonresponse, where an individual loses the benefit of a previously effective therapy. Hypersensitivity reactions also occur, such as infusion reactions as- sociated with anti-infliximab ADAs, but anaphylactic reactions are fortunately rare. Soluble receptors are less immunogenic as they contain minimal foreign sequence. Immunogenicity is influenced by many factors such as the primary mAb sequence, its formulation (particularly the presence of aggre- gates), the route of administration and precise treatment regime, disease under treatment, and coadministered therapy. For example, anti-TNF mAbs are more immunogenic in rheumatoid arthritis than in ankylosing spondylitis or psoriatic arthritis; and the frequency of ADAs in rheumatoid arthritis patients is reduced by coadministration of methotrexate. Even with such cotherapy, however, almost a third of patients receiving the fully human mAb adalimumab generated ADAs, most commonly within the first 6 months of therapy, which significantly reduced efficacy. Measurement of circulating drug is often easier than measuring ADAs, and a number of algorithms have been proposed whereby measurement of drug levels with or without ADAs should render mAb therapy more personalized and cost- effective. Nonetheless, controlled trials with economic analyses are ideally needed before so-called 'therapeutic drug monitoring' can be recommended in routine practice. Biosimilars The availability of biological therapies has been restricted or ra- tionalized in most parts of the world, due in large part to their high cost. However, as the patents protecting the original biological drugs expire, there is the potential for biosimilar molecules to be developed at lower cost. Unlike synthetic small molecule drugs, it is not possible to create an exact replica of a therapeutic mAb. This is because many features, particularly post-translational modifica- tions, depend less on the primary amino acid sequence and more on cell culture conditions and downstream manufacturing, pro- cessing, and production. Furthermore, some of these features are difficult to characterize precisely, and a given batch of therapeutic mAb is also characterized by 'microheterogeneity'—a mixture of closely related but distinct molecules. Consequently, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have developed regulations for the development of biosimilar biological products. These rely

heavily on in vitro com- parisons of the physicochemical characteristics and biological ac- tivities of the originator and biosimilar biologicals, and less on data from clinical trials in humans. While reducing the cost of biosimilar development these guidelines mean that biosimilars can be licensed having been administered to relatively few patients. Because it is im- possible for a biosimilar to be identical to the originator biological, this limited clinical experience has led to concerns over safety and efficacy. There are additional questions around: indication extrapo- lation (biosimilars can be licensed for the same indications as the originator biological without requiring clinical trial data in each indication); differences in immunogenicity compared to the ori- ginator biological; substitution (the potential for a pharmacist to substitute a biosimilar when an originator biological has been pre- scribed); nomenclature and identification of the biosimilar product, particularly when adverse effects occur. While smaller and less complex than mAbs, biosimilar growth factors have been marketed for several years without significant problems. Furthermore, there is batch-to-batch variability of originator biologicals, particularly when manufacturing processes change. Nonetheless the launch of biosimilar mAbs has been seen as a major milestone and a number of anti-TNF and rituximab biosimilars are now licensed and in use, so far without unexpected complications. Future developments Stratified medicine There are currently four classes of biological therapy for rheumatoid arthritis: anti-TNF, anti-IL-6R, B-cell depletion, and costimulation blockade. Surprisingly, the efficacy profile of each class is very similar, with only 10–20% of established rheumatoid arthritis patients achieving optimal responses. Adverse event profiles are also largely similar. Currently, however, there are no biomarkers available that help the rheumatologist decide which biological class to try first in a particular patient. A similar situation pertains to TNF blockade, anti-p40 blockade, and integrin blockade in IBD. Because biological therapies are costly this has negative health economic implications as well as delaying the achievement of disease control, which may require cycling through more than one agent. Consequently, there has been a major investment in the identification of ‘stratifiers’ to guide therapy examining, for example, genetics, transcriptional and proteomic profiles in blood and, particularly in IBD, tissue charac- teristics. In cancer the tissue often provides a clue, such as the use of trastuzumab in HER2 positive breast cancer. In the respiratory field omalizumab (humanized anti-IgE) is indicated in allergic asthma pa-tients who have a positive skin test or in vitro reactivity to a perennial

 aeroallergen, and dosed according to serum IgE levels. Mepolizumab (humanized anti-IL-5) is indicated only for patients with refractory eosinophilic asthma. Once stratifiers are identified, new tests (com- panion diagnostics) will be developed to assist in the most appro- priate allocation of therapy. Antibody fragments and novel species Novel species include bispecific antibodies, which can now be pro-duced using various technologies, as well as smaller antibody frag- ments. Bispecific antibodies permit the simultaneous targeting of two specificities by a single molecule. In inflammatory diseases, for example, there is significant interest in the dual targeting of TNF and IL-17. Smaller antibody fragments, while suffering from a shorter half-life, should achieve better tissue penetration. This will be par- ticularly important not only in oncology, but potentially also in in-flammatory diseases. FURTHER READING Baker KF, Isaacs JD (2018). Novel therapies for immune-mediated in- flammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn’s disease and ulcerative colitis? Ann Rheum Dis, 77, 175–87. Beniwal-Patel A, Saha S (2014). The role of integrin antagonists in the treatment of inflammatory bowel disease. Expert Opin Biol Ther, 14, 1815–23. Billiet T, et al. (2014). Targeting TNF-α for the treatment of inflamma- tory bowel disease. Expert Opin Biol Ther, 14, 75–101. Dörner T, Kay J (2015). Biosimilars in rheumatology: current perspec- tives and lessons

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