Clinical Immunology

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Designer drugs: the biologic therapies

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Following the development of hybridoma-derived monoclonal antibodies (mABs) in the 1970s major advances have been made in monoclonal and fusion protein therapeutics. This has coincided with a rapid expansion in the understanding of disease and immune pathogenesis. As molecular understanding of many disease processes becomes clear, it is logical to target the key components defined in disease pathogenesis. For example, tumour necrosis factor (TNF) α has been identified as a major cytokine in the pathogenesis of rheumatoid arthritis (RA) and Crohn's disease. By harnessing this knowledge of disease pathogenesis with the ability to produce specific therapeutic agents, treatments can be directed in a more focused way. When used alongside conventional therapies and applied early, these agents give the opportunity to modify disease course and help to limit the side effects of standard therapy.

This review focuses on the biology and current clinical applications of these new therapeutics, some of which are well established while others are just beginning to impact on many areas of clinical medicine.

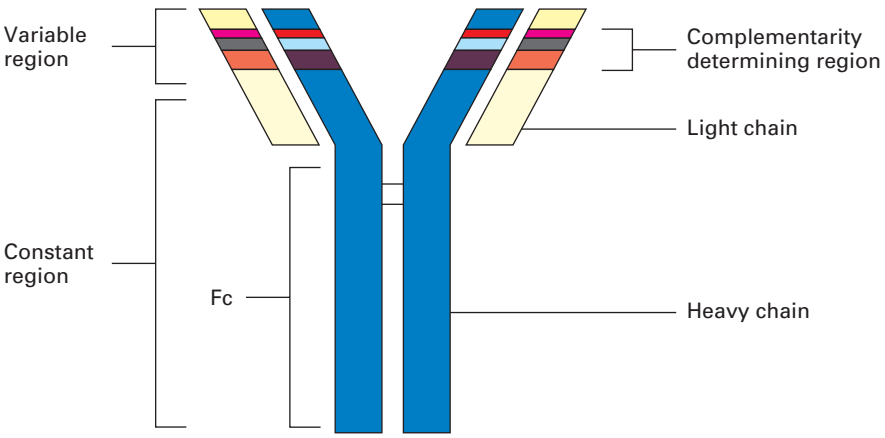

Fig 1. Antibody structure. Each antibody consists of two identical heavy and light chains, arranged as a Y-shaped tetramer, with each chain arranged into variable and constant regions. The variable regions are the site of antigen binding, specifically the complementarity determining regions, the amino acid sequence of which confers the antigen binding specificity. The heavy chain constant region determines antibody function.

Biology

The immune system is designed to protect the host from infection and can direct specific responses against a wide range of antigens. One of the most important features of the adaptive immune system is its specificity. When B lymphocytes are activated they differentiate into antibody secreting plasma cells, each B cell clone producing an antibody with a single antigen binding specificity (ie an mAB).

Antibodies consist of two identical heavy and light chains, each composed of variable and constant regions (Fig 1). The antigen binding specificity is determined by the amino acid composition of the complementarity determining regions which lie at the distal most end of the variable domains. Variations in the amino acid sequence at this site lead to the great diversity in antibodies that can be generated. The constant domain (Fc) determines antibody function, while structure determines isotype (eg immunoglobulin (Ig) G, IgM). Antibody functions include complement activation, immune complex clearance and antibody-dependent cellular cytotoxicity, the last being a potent way by which cellular targets labelled by therapeutic mABs undergo lysis.

Hybridoma technology was first developed by Köhler and Milstein in the early 1970s.[1] Hybridomas were developed by the immunisation of mice, the resultant B cells being subsequently fused with murine myeloma cell lines (and thus immortalised) to form the hybridoma. The clones could then be selected for those producing the antibody of interest and produced in unlimited quantities. Despite huge interest, it took almost another 10 years before therapeutic mABs reached the clinic. Muromonab-CD3 was the first to be approved in 1986 (see below). The development of human anti-mouse antibodies was a significant limiting factor for some of the early murine treatments.

Genetic engineering has opened new perspectives for the selection and production of mABs, avoiding the need to immunise laboratory animals. Developments have led from the production of murine through chimaeric and human-

Table 1. Monoclonal antibody (mAB) designation.

Antibody type	Definition
Monoclonal	Originally defined as an antibody produced from a single B cell clone. Genetic manipulation now allows the combination of genes from different B lymphocyte sources (eg mouse and human) Specific mABs have identical antigen binding regions and bind to the same antigenic epitope
Murine	mAB derived from a purely mouse source, murine hybridomas developed from fusion of murine B lymphocyte with murine myeloma cell
Chimaeric	mAB derived from combination of murine variable region with human constant region genes
Humanised	mAB derived from combination of murine complementarity determining region genetic material with the remainder of the antibody genetic material of human origin
Human	mAB derived entirely from human sources (eg transgenic mice or phage display)

ised and now to fully human mABs (Table 1, Fig 2). Advantages include:

- improved interaction with human Fc receptors on effector cells, hence improved effector function
- reduced immunogenicity, thus prolonging the therapeutic half-life and reducing adverse reactions particularly on repeat exposure.

The selection of a specific Fc component allows the function of the antibody to be determined (eg target cell lysis versus binding and inhibition of a cell surface molecule). There are two types of mABs:

- depleting, eliminating the target cell type
- non-depleting, blocking the activity of the target.

They can also be labelled with additional components: for example toxins for use in cancer immunotherapy. Nomenclature of monoclonal antibodies is set out in Table 2.

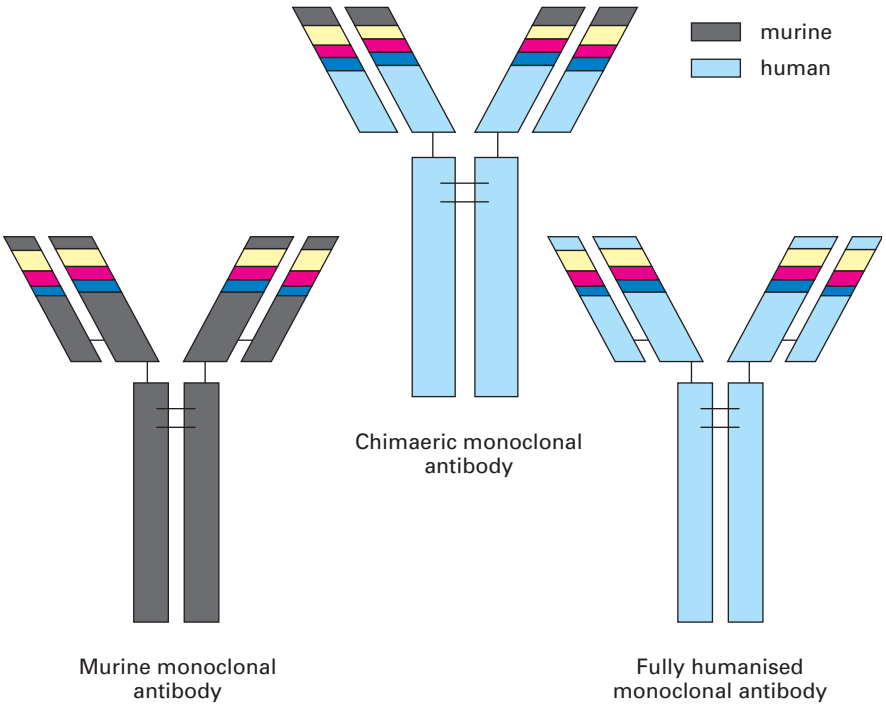

Fig 2. Monoclonal antibody (mAB) construction. The different components of the antibody structure can be derived from different genetic sources. Chimaeric mABs are generally derived from murine variable region genetic sequences combined with constant region genes of human origin. Fully humanised mABs are composed of murine complementarity determining regions with the rest of the antibody of human genetic origin. Human mABs are produced from entirely human genetic sequences (Table 1).

Fusion proteins are generated by the combination of a specific molecular component (eg cell surface receptor) to the Fc backbone of a human antibody molecule, usually IgG1, allowing integration of the antibody effector function with the molecular component of interest (Fig 3). A well known example is etanercept, a recombinant fusion protein of human TNF receptor 2 with IgG1 Fc.

Specific areas of clinical application

Biologic therapies directed against many different molecular components are entering the clinical arena. Full details of the current US Food and Drugs Administration (FDA) approved and European Medicines Agency (EMEA) authorised therapeutic biologic agents can be found at www.fda.gov and www.emea.ev.int (see summary of product characteristics).

Inflammatory bowel disease (IBD)

Infliximab (anti-TNFα mAB) has shown clinical benefit in patients with moderate to severely active intestinal Crohn's disease. It is licensed for patients whose disease is resistant to conventional therapies. Infliximab is efficacious in the treatment of Crohn's related fistulas[2] and for the induction and maintenance therapy for moderate to severe ulcerative colitis (UC), but remains unlicensed for UC.[3]

mABs targeting the α_4 integrins as 'selective adhesion molecule inhibitors', preventing leucocyte migration into

inflamed tissue, have been reported in Crohn's disease and UC[4,5] but, in addition to limited efficacy, major concerns about safety have been reported (see below).

Rheumatoid arthritis

The combination of etanercept or infliximab with methotrexate is safe, well tolerated and efficacious in patients with persistently active RA,[6,7] with early use beneficial.[8] Etanercept is licensed to use alone or in combination with methotrexate in patients with moderate to severely active RA, including those not previously treated with methotrexate. Infliximab is licensed for use with methotrexate.

The National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of these agents for the treatment of RA in 2002.[9] Adult patients with active disease must have failed with at least two standard disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated). Adalimumab is also licensed.

Other biologics with reported efficacy in RA include the modified CTLA4-Ig fusion protein abatacept,[10] which blocks T cell costimulation (Fig 4) and the anti-CD20 mAB rituximab[11] which selectively targets B lymphocytes.

Dermatological disease

Etanercept and infliximab are licensed for chronic plaque psoriasis, supporting TNFα as a major disease cytokine. Two adhesion molecule blockers have also been approved for this indication:

- alefacept, a fusion protein of human LFA3-IgG1 Fc which targets CD2 on T lymphocytes, and
- efalizumab, a humanised mAB that binds to the α subunit of LFA-1 and inhibits T-cell activation.

Other systemic autoimmune conditions

Etanercept has been investigated for the treatment of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis in which TNFα is thought to play a pathogenic role. The Wegener's Granulomatosis Etanercept Trial (WGET)[12] found that etanercept was not effective for maintaining remission in patients with Wegener's granulomatosis, durable remissions were achieved in only a minority and there was a high rate of treatment related complications. In addition, the rate of solid tumours was increased in the etanercept treated group. The authors postulated that the combi-

Table 2. Monoclonal antibody (mAB) nomenclature.

The nomenclature of mABs is based on the following convention:
Prefix – disease/target class – animal source – suffix

Prefix	Disease/target class	Animal source	Suffix
To create a unique name, a distinct syllable is selected as the starting prefix	Viral – *vir-* Bacterial – *bac-* Immune – *lim-* Infectious lesions – *les-* Cardiovascular – *cir-* Tumours: Colon – *col-* Melanoma – *mel-* Mammary – *mar-* Testis – *got-* Ovary – *gov-* Prostate – *pr(o)-* Miscellaneous – *tum-*	The following letters identify the animal source: *u* – human *o* – mouse *a* – rat *e* – hamster *i* – primate *xi* – chimaeric *zu* – humanised	*-mab* is used both for mABs and fragments

When combining the target or disease infix with the source stem for chimaeric monoclonals, the last consonant of the target disease syllable is dropped:

eg abciximab
target = *cir*, source = *xi*, *-mab* stem
daclizumab
target = *lim*, source = *zu*, *-mab* stem

If the product is radiolabelled or conjugated to another chemical such as a toxin, identification of the conjugate involves use of a separate second word or other chemical designation. If a toxin is used, the *–tox* stem must be included in the name selected for the toxin.

Fusion protein nomenclature includes the suffix – *cept*

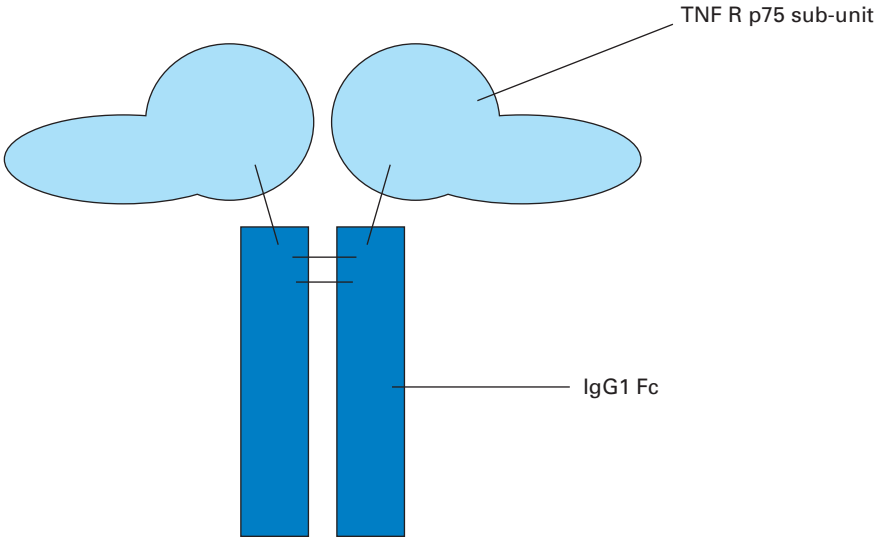

Fig 3. Fusion protein construction. Combination of the molecular component of interest with the Fc region of an antibody molecule, usually immunoglobulin (Ig) G1 Fc, imparts the Fc function on to the component for therapeutic use. Etanercept, the example shown here, incorporates human IgG1 Fc on to two recombinant tumour necrosis factor receptor (TNF R) p75 subunits, thereby acting as a TNFα blocking agent.

Key Points

- Therapeutic biologics (monoclonal antibodies and fusion proteins) can target specific molecular components involved in disease pathogenesis, allowing disease focused treatment
- Therapeutic biologics have a significant role to play across the spectrum of clinical medicine
- Many agents are already licensed for clinical use
- In those conditions where such therapy is not licensed, but logical according to disease mechanism, a therapeutic trial can be considered in treatment refractory cases. Informed consent is then crucial
- Safety and cost are important considerations

KEY WORDS: antibody, chimaeric, fusion protein, humanised, hybridoma, monoclonal, therapeutic

nation of TNFα inhibition and cyclophosphamide may heighten the cancer risk beyond that of cyclophosphamide alone. Infliximab has been successful in ANCA-associated vasculitis[13] but infection risks are a concern.

An area of increasing interest is the use of rituximab in disorders where autoantibodies are believed to play a pathogenic role. In addition to ANCA-associated vasculitis, rituximab has been used successfully in the treatment of cryoglobulinaemic vasculitis and systemic lupus erythematosus (SLE).[14,15] Treatment with rituximab in 100 patients with severe, treatment-refractory SLE in 2005 demonstrated that 80% achieved marked and rapid reductions in global disease activity. Double-blind studies comparing rituximab with existing immunosuppression are needed in this context.

Natalizumab, an mAB directed against α_4 integrins, has been used in multiple sclerosis (MS) and IBD. All administration was voluntarily suspended in 2005 following reports of progressive multifocal leukoencephalopathy (PML).[16–18] Outcome data published in March 2006, following two years of natalizumab therapy in relapsing MS suggest clinical benefit.[19] An evaluation of 3,116 natalizumab treated patients suggested a risk of PML in the order of one in 1,000 patients treated for a mean of 17.9 months.[20] The longer-term risk is obviously unknown. In February 2006 the FDA approved further administration of natalizumab to patients with relapsing-remitting MS who had previously been treated in clinical trials.

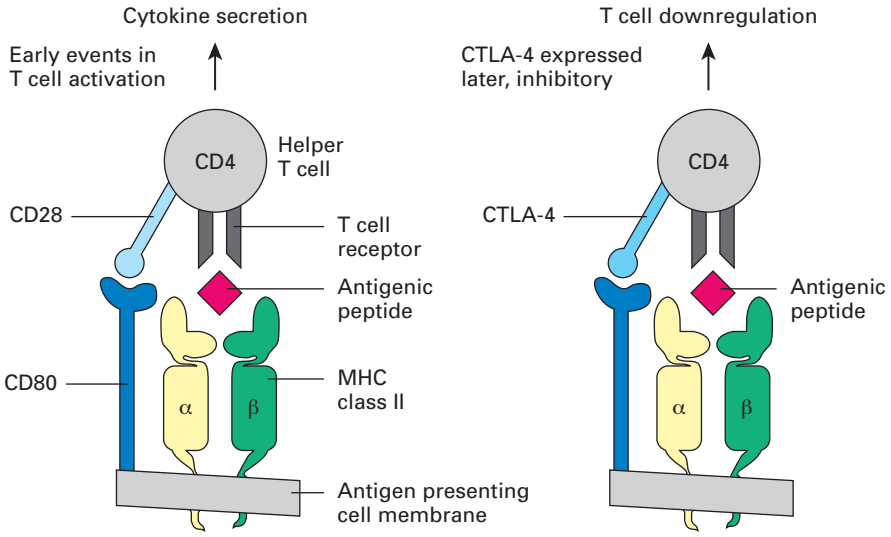

Fig 4. T cell costimulation and costimulatory blockade. For activation, T cells require interaction between the T cell receptor with antigenic peptide presented in the context of self-major histocompatibility complex (MHC) by the antigen presenting cell (APC). A second 'costimulatory' signal is required for full activation, delivered by the interaction between CD28 on the T cell with CD80/86 on the APC. Later, the T cell expresses CTLA-4, which has higher affinity for CD80/86 and delivers a downregulatory signal, to 'switch off' the immune response when pathogen is cleared. Fusion proteins based on the CTLA-4 structure have been developed to block the costimulatory pathway, for use in autoimmunity and transplant rejection.

Transplantation

Muromonab-CD3, a murine mAB directed against T cell CD3 surface glycoprotein, was approved for the treatment of acute renal transplant rejection in 1986. Its licence was extended to acute cardiac or hepatic transplant rejection in patients resistant to standard therapy. Daclizumab and basiliximab, mABs directed against CD25, the α subunit of the interleukin (IL)-2 receptor expressed on activated T lymphocytes, were approved for use in 1997 and 1998, respectively. (IL-2 can be regarded as the predominant cytokine stimulating T cell division). Daclizumab has been shown to reduce the frequency of acute rejection in renal transplant recipients,[21] and induction therapy with daclizumab reduces the frequency and severity of cardiac allograft rejection during the induction period.[22]

Other immunosuppressive regimens continue to be investigated. The role of costimulatory blockade, most recently belatacept, a fusion protein derived from abatacept, was shown to have similar efficacy to ciclosporin in preventing acute rejection after renal transplantation.[23]

Malignancy

Rituximab was first licensed for use in the treatment of B cell non-Hodgkin's lymphoma in 1997. Additional therapies for B cell malignancy include ibritumomab and alemtuzumab (anti-CD52).

Radionuclide-labelled mABs given systemically can potentially deliver cytotoxic doses of irradiation to sites of disseminated disease, targeted by the specific antigen recognition properties. ^{131}I-tositumomab targets CD20 on normal and malignant B cells. This is of benefit in patients with follicular lymphoma who relapse after chemotherapy or whose disease is treatment refractory. Alemtuzumab is used in a variety of protocols for conditioning pre-bone marrow transplant, although this use remains unlicensed.

Trastuzumab (Herceptin), a humanised mAB directed against human epidermal growth factor receptor (HER2) increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2.[24] Cetuximab, an mAB directed against epidermal growth factor receptor, is licensed for use in combination with irinotecan in metastatic colorectal malignancy. Bevacizumab, an mAB directed against vascular endothelial growth factor, is also licensed for this indication.

Table 3. Warnings concerning the use of biologic therapies.

Consult summary of product characteristics.

Biologic agent	Specific warnings
Adalimumab (Humira)	Risk of infection, especially TB Patients should be assessed for active/latent TB before treatment Treatment of latent TB initiated prior to adalimumab therapy, contraindicated in active TB
Alemtuzumab (MabCampath)	Haematologic toxicity ITP alert November 2005 Infusion reactions Infection/opportunist infection
Basiliximab (Simulect)	Administered only by physicians experienced in immunosuppressive treatment and management of organ transplantation Facilities must be equipped staffed with adequate laboratory supportive medical resources
Bevacizumab (Avastin)	GI perforation Wound healing complications Haemorrhage
Cetuximab (Erbitux)	Infusion reactions
Daclizumab (Zenapax)	Administered only by physicians experienced in immunosuppressive treatment and management of organ transplantation Facilities must be equipped staffed with adequate laboratory supportive medical resources
Etanercept (Enbrel)	Infection
Ibritumomab tiuxetan (Zevalin)	Fatal infusion reactions Prolonged and severe cytopenias
Infliximab (Remicade)	Risk of infection, especially TB Patients should be assessed for active/latent TB and treatment initiated prior to infliximab therapy, contraindicated in active TB Invasive fungal and other opportunist infections Hypersensitivity reactions
Palivizumab (Synagis)	Anaphylaxis (rare)
Rituximab (MabThera)	Infusion reactions Tumour lysis syndrome Severe mucocutaneous reactions
Tositumomab Iodine I-131 tositumomab (Bexxar)	Hypersensitivity reactions Prolonged and severe cytopenias
Trastuzumab (Herceptin)	Cardiomyopathy, especially when given with anthracyclines and cyclophosphamide

GI = gastrointestinal; ITP = idiopathic thrombocytopenic purpura; TB = tuberculosis.

Cardiovascular indications

Abciximab, a chimaeric mAB Fab fragment directed against platelet glycoprotein (GP) IIb/IIIa receptor, reduced by 35% the incidence of acute ischaemic events among patients undergoing 'high-risk' percutaneous coronary revascularisation,[25] but at the expense of increased haemorrhagic complications. Subsequent studies have investigated abciximab combined with lower-dose heparin. NICE guidance recommends that a GP IIb/IIIa inhibitor should be considered in the management of unstable angina or non-ST-segment elevation myocardial infarction.

Infectious disease

Palivizumab, a humanised mAB directed against the F protein of respiratory syncitial virus (RSV), is the only mAB licensed for the prevention of infectious disease. It is indicated for the prevention of RSV infection in infants at high risk.

Allergic disease

Treatment with an anti-IgE mAB in 317 patients with moderate to severe allergic asthma showed potential benefit. More subjects in the active treatment arms were able to decrease or discontinue use of corticosteroids than in the placebo group.[26] Omalizumab is now licensed for use in adults and adolescents with severe persistent atopic asthma whose symptoms are inadequately controlled with inhaled corticosteroids and long-acting beta 2-agonist.

Biologics: warnings and therapeutic considerations

Certain warnings and considerations apply to biologic therapies (Tables 3

Table 4. Therapeutic considerations.

When considering the use of a biologic therapy the following points should be addressed:

1. Is the condition a licensed indication?
2. Has the patient failed conventional therapy?
3. Is there a suitable alternative?
4. If used for an unlicensed disease:
   - does the disease pathogenesis make such therapy logical?
   - is it justified?
   - does the patient understand and consent to unlicensed treatment?
5. Is there guidance to help in the decision (eg NICE)?
6. What is the cost of treatment versus hospital bed occupancy and other factors (ie the cost of using versus not using the biologic)?
7. What are the selection/registration/monitoring requirements?

and 4). The summary of product characteristics should be consulted when considering patients for treatment with biologics.

The British Society for Rheumatology (BSR) set up the BSR Biologics Registry in 2000.[27] In addition to recording data on treated patients, the Registry has two specific roles:

1. To answer whether biologic therapy is safe in the short- and long-term.
2. To have a formal pharmacovigilance role.

As experience accumulates and safety issues are addressed, the need for registration may subside. Indeed, registration for etanercept was completed in May 2005. The importance of ongoing monitoring cannot be overemphasised. Tuberculosis has been recognised as a particular risk with the use of anti-TNFα therapies, natalizumab has been associated with PML, and other specific complications continue to be reported. Clearly, treatment must not be a greater risk to the patient than the underlying disease.

Cost is the other major consideration when broadening clinical applications. These agents are expensive to develop and subject to the necessary rigours of clinical trials. When approved and licensed, they are expensive to use in the clinic, hence certain indications are explicit concerning treatment of refractory disease. To the individual, the cost of not treating also has to be considered and treatment of refractory disease makes this consideration all the more important.

Conclusions

The advances in biologic therapies have resulted from greater understanding of immune mechanisms and disease pathogenesis, combined with developments in drug design. The aim of such therapy is to be disease-specific. As experience accumulates, criteria for appropriate application and safety emerge. Cost is a significant consideration, therefore careful patient and disease selection is of utmost importance.

The final comment by Köhler and Milstein in their original paper on hybridoma development was that 'such cultures could be valuable for medical and industrial use'.[1] They cannot have anticipated the enormous impact their work would have across the spectrum of clinical medicine.

Acknowledgement

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Therapeutic apheresis – plasmapheresis

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Background

Apheresis is derived from the Greek, meaning 'withdrawal'. Blood components can be separated by either filtration or centrifugation (Fig 1). Filtration systems allow plasma removal (plasmapheresis) with retention of blood cells. Centrifugal systems are more versatile, allowing plasmapheresis or selective removal of cell types (eg plateletphoresis). Blood components (eg HLA-matched platelets or bone marrow derived 'stem cells') can be 'withdrawn' from healthy volunteers for patient treatment. This article focuses on the removal of pathogenic/abnormal blood constituents.

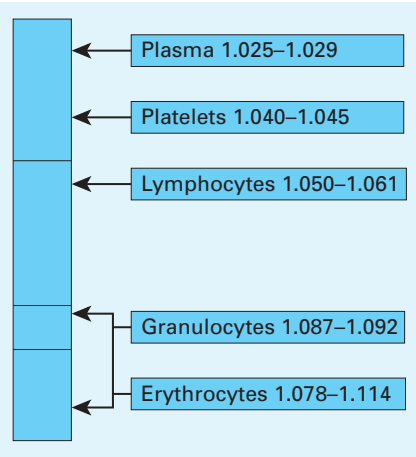

Fig 1. Blood components, separated by centrifugation according to relative density.

Typically, plasmapheresis is an emergency intervention, effective for only a few days unless parallel treatment for the underlying condition is instituted. Plasmapheresis buys time whilst immunosuppression takes effect. Where possible, the patient travels to the treatment centre, but the staff and machine may need to travel to the bedside for sick patients.

Continuous versus intermittent flow apheresis machines

Continuous flow separators (Fig 2) retain healthy blood components and separate plasma for disposal. Using a double-needle kit, blood enters one limb and returns post-centrifugation and plasma removal via another. Continuous fluid replacement maintains isovolaemic balance. The extracorporeal circuit volume is minimal (<150 mol), but none the less large for babies and small infants.

Key Points

Plasma removal (plasmapheresis) directly removes pathogenic autoantibodies and other plasma factors (eg cytokines) to provide temporary therapeutic benefit

Relapse is likely without concurrent immunosuppression and/or other appropriate treatment of the underlying condition (preventing autoantibody production)

Plasmapheresis is a limited resource, largely limited to regional centres; it requires staff experienced in use of specialist apheresis machines

Alternative treatments should be used first (eg Guillain–Barré syndrome for which intravenous immunoglobulin therapy is equally effective)

Commoner side effects relate to central-line insertion, loss of plasma clotting factors and hypocalcaemia caused by citrate anticoagulation

KEY WORDS: autoantibody, immunosuppression, plasmapheresis, vasculitis