Recent advances in understanding the immunopathogenesis of autoimmune rheumatic diseases have led to novel therapeutic strategies. Prominent amongst these is the use of monoclonal antibodies (mAbs) to modulate the immune system via a number of target molecules. These include components of the trimolecular complex (HLA molecules and the T cell receptor), and lymphocyte surface markers such as CD4, CD5 and CD7. Encouraging data from experiments using such reagents in animal models of autoimmune disease have led to clinical trials. To date these have mainly been conducted in patients with rheumatoid arthritis. Anti-CD4 mAbs are effective but only produce a long-term clinical improvement in 10% of patients. An immunotoxin CD5plus is clinically effective, particularly in early disease. However, anti-CD7 mAbs produced no clinical benefit. The majority of these studies are uncontrolled involving small numbers of patients, and comparison with conventional therapy is lacking. Rodent mAbs are immunogenic in man producing an anti-globalin response, which may prevent repetitive therapy. Development of chimeric or humanized mAbs (such as CAMPATH I) which ought to be less immunogenic should enable this problem to be overcome. Indeed early data suggest that this is so. Other new approaches include T cell vaccination and the use of peptides to block binding of HLA molecule to antigenic peptide. T cell vaccination has been tried in rheumatoid arthritis with modest results, but formidable problems remain to be overcome before this therapy becomes widely applicable. Clearly many innovative therapies for autoimmune disease are currently being developed and immunotherapy will be prominent amongst these.
The immunopathogenesis of the autoimmune rheumatic diseases is increasingly well understood. At present it is believed that an autoantigenic peptide is presented by an appropriate human leucocyte antigen (HLA) to a receptor on an autoantigen specific T cell; these three molecules comprise the trimolecular complex. Activation of T cells specific for the autoantigen results in stimulation of further immune and non-immune effector mechanisms. The T cell receptor (TCR) is composed of two chains α and β or γ and δ, each of which has a variable region (V) similar to that on an immunoglobulin molecule. It is unclear whether the T cell response in human autoimmune disease is polyclonal or as in some animal models restricted. Advances in molecular biology have led to the development of novel therapeutic approaches. Prominent amongst these are monoclonal antibodies (mAb) which enable specific cell subsets, surface molecules and secreted products, to be selectively identified and their function modulated. Other approaches include T cell vaccination, blockade of the major histocompatibility complex (MHC) and immunotoxins. This review will concentrate on rheumatoid arthritis (RA) because there is relatively little data on immunotherapy in other autoimmune rheumatic conditions.

There is now evidence that T lymphocytes, in particular the CD4+ (helper) subset are important in the initiation and maintenance of rheumatoid inflammation. Treatment with non-specific immunomodulating drugs, however, is often unsatisfactory due to poor efficacy or frequent side-effects. Early attempts at reducing lymphocyte numbers involved thoracic duct drainage, lymphocytapheresis, nodal irradiation and antithymocyte globulin. These therapies were all capable of inducing a transient clinical remission, but their associated toxicity or impracticability prevented widespread use. Cyclosporin A (a fungal peptide which modulates cytokine production by T cells) has been used in several trials resulting in clinical improvement but associated nephrotoxicity has limited widespread use.

Monoclonal Antibodies

Monoclonal antibodies provide a novel approach to the immunotherapy of autoimmune and inflammatory disorders. By targeting specific antigens on lymphocytes they are able to destroy them, or modulate their function. Monoclonal antibodies may exert their influence on the immune system in two ways (1) immunosuppression and (2) tolerance induction.

Monoclonal antibodies have been used to prevent or ameliorate inflammatory arthritis in several animal models of RA. Ranges and colleagues first demonstrated that administration of anti-CD4 mAbs prior to immunization of mice with type II collagen reduced both the incidence and severity of arthritis. Similar results have been obtained with mAbs directed against MHC class Ia and the interleukin 2 receptor (IL-2-R) given either before or at the time of immunization. However, no effect was seen when the mAb was given after immunization with collagen. Furthermore, anti-CD4, anti-CD8 mAbs alone or in combination had no effect on established disease. Monoclonal antibodies against the α and β chains of the TCR are capable of completely preventing collagen-induced arthritis in rats when administered at the time of immunization with collagen, and if treatment is begun after the onset of arthritis able significantly to suppress the disease. This suggests that T cells have a role in the maintenance of the disease as well as in induction. More recently attempts have been made successfully to modulate murine collagen-induced arthritis using antibodies against specific TCR Vβ chains. Thus Vβ specific mAb may constitute a useful set of reagents to eliminate autoimmune T cells.

The leucocyte function-related antigen-1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1) interaction is important in neutrophil migration to sites of inflammation. CD18 is a component of LFA-1, anti-CD18 mAbs modify the acute arthritis of antigen induced arthritis in rabbits (a model of RA) and also ameliorates the subsequent chronic inflammation. Anti-ICAM-1 mAbs are also effective at suppressing development of arthritis and reducing inflammatory parameters. Modulation of the immune system using idio- and anti-idiotype has been proposed as a therapeutic approach in the management of autoimmune disease. In New Zealand black/white mice (a model of systemic lupus erythematosus) anti-idiotypic mAb administration has been shown to suppress both production of anti-DNA antibodies and nephritis, however, the effect was transient and anti-DNA antibodies appeared that did not bear the idiotyp. Conjugation of anti-idiotypic mAb to a cytotoxic agent (neocarzinostatin) has been shown to eliminate anti-DNA antibody producing cells in vitro. Modulation of the DNA idio-type-anti-idiotype network will perturb other idio-type-anti-idiotype systems.
It must be remembered that such manipulation may induce disease rather than suppress it.

Until recently, the use of mAbs in inflammatory arthritis had been confined to animal models, but a number of small open studies in man have now been reported which reveal potent anti-inflammatory effects. Three main antigen targets have been considered: (1) pan T cell antigens, (2) CD4, and (3) T cell activation antigens.\textsuperscript{11}

**Pan T Cell Antigens**

Although anti-CD3 mAbs are available and have been shown to be safe in the treatment of renal allograft rejection,\textsuperscript{20} they have not so far been used in RA. Antibodies against CD5 and CDw52 (the CAMPATH antigen\textsuperscript{21}) target all mature T cells. The CD5 antigen is also present on a subset of B cells believed to play an important role in the pathogenesis of RA\textsuperscript{22} whilst CDw52 is present on lymphocytes (B and T cells) and some monocytes.\textsuperscript{21} A total of 95 patients has now been treated with CD5plus, a murine anti-CD5 antibody linked to the ricin A chain (a potent plant toxin that inhibits protein synthesis) to enhance cytolitic effects. In a phase II study 41/79 patients were improved by $\geq 50\%$ in 4/6 clinical parameters 1 month after therapy. Seventeen patients were improved at 6 months and six patients at 10 months.\textsuperscript{23} Preliminary data from this study suggests that the mAb is particularly effective in early disease (failure of methotrexate treatment, mean disease duration 1.9 years) compared with late disease (failure of multiple second-line drugs, mean disease duration 10.8 years).\textsuperscript{24} The role of the ricin A chain in the clinical response is uncertain, as no data are available regarding the unconjugated antibody. CAMPATH 1H is the first humanized mAb to be used clinically. This antibody produced a significant improvement in eight of nine patients in Ritchie articular index and joint score which lasted for up to 6 months.\textsuperscript{25,26} Profound lymphopaenia (CD4, CD8, B cells) was induced which lasted for up to 1 year.

**T Cell Activation Antigens**

Activation antigens are present on T cells following stimulation by antigen and should, therefore, include the self-reactive clones in autoimmune disease. Further focusing the immune attack antibodies against them ought to result in less immunosuppression than seen with CD4 mAbs. CAMPATH 6, a rat antibody directed against the IL2-receptor (CD25), produced a 3-month improvement in two of three patients treated.\textsuperscript{38} Conversely murine and chimeric mAbs against CD7, an activation antigen of unknown function, did not lead to major improvements in 16 patients treated.\textsuperscript{39,40}

**Other Autoimmune Rheumatic Disease**

Mathieson and colleagues reported a patient with a 25-year history of a vasculitic illness characterized by fever, skin rash, arthritis, myalgia, pericarditis, pleurisy and episcleritis.\textsuperscript{41} Histology of the skin and muscle demonstrated a vasculitis with prominent lymphocyte infiltrate. This illness had only been partly controlled by conventional immunosuppressive agents. A course of therapy with CAMPATH 1H resulted in an impressive improvement in symptoms, however, this was of short duration. Two further courses resulted in similar transient improvement. A more durable remission was achieved using a course of CAMPATH 1H followed by a course of rodent anti-CD4 mAb.

Four patients with lupus nephritis have been treated with CD5plus, and evidence of improvement in renal function was observed in three patients 5 months after therapy.\textsuperscript{42} A single case
Complications of Antibody Therapy

Rodent antibodies usually provoke an anti-globulin response in a human recipient, and the above trials have confirmed this. Although this complication has not prevented second courses of treatment, these may be less effective and importantly, may result in potentially dangerous reactions. Genetic engineering has led to the development of recombinant antibodies, either chimeric (rodent variable region in association with a human constant region) or fully humanized (in which only the complementarity determining regions of the mAb remain foreign). Trials of a chimeric anti-CD4 mAb and an anti-CD7 mAb suggest that as anticipated the incidence of an anti-globulin response was lower following the use of chimeric mAbs compared with murine mAbs. An anti-globulin response was not observed in the patients treated with a single cycle of CAMPATH 1H. Whether the more complicated process of humanization is more effective than chimerization is at present unknown.

Although potently immunosuppressive, mAbs have not thus far been associated with a high incidence of infection, when used alone. When they do occur, infections are usually of viral origin and seen in association with concurrent immunosuppressive therapy.

There is an increased incidence of malignancy in patients receiving OKT3 (an anti-CD3 mAb) for transplant rejection. Again, this appears to relate to the overall degree of immunosuppression, rather than antibody therapy alone. Nonetheless, this factor must not be forgotten, particularly in the younger patient.

Immunotoxins

Immunotoxins are a means of directly delivering toxic molecules to target cells. The CD5 mAb ricin conjugate has already been discussed. The IL-2 receptor has been targeted using a genetically engineered fusion protein comprising the toxic component of the diphtheria toxin and IL-2 (DAB_{486} IL-2). Thus the toxin is delivered directly to activated T cells bearing the IL-2 receptor. In the rat adjuvant arthritis model, animals treated with DAB_{486} IL-2 during the induction phase of disease had delayed onset of symptoms and decreased severity of inflammation as well as a depressed proliferative response to mycobacterial stimulation in vitro. Thirteen patients have been treated in an open uncontrolled trial with transient benefit in most.

T Cell Vaccination and anti-TCR Therapy

T cell vaccination either with intact though inactivated T cells or with peptides derived from T cell receptors is an alternative to mAb therapy. The idea is to induce specific immunity to disease specific T cells possibly invoking idiotypic networks. Preliminary data suggest that this approach may result in modulation of disease activity, but there are major problems to be overcome if this technique is to become clinically useful. Elimination of autoreactive TCR gene products by mAbs is an attractive possibility. Collagen arthritis can be modulated by mAbs directed against specific TCR Vβ chains leaving the remainder of the T cell repertoire intact. The T cell response in RA and SLE appears not to be oligoclonal and, therefore, it is difficult to direct mAb against RA specific T cells. It is encouraging that anti-αβ TCR mAbs can modulate the course of established adjuvant arthritis, since in human disease, treatment will inevitably be begun after triggering of the immune response.

Anti-MHC Therapy

The association between autoimmune disease and human HLA class II alleles (e.g. DR4 and DR1 in RA) has suggested a further approach for immune intervention by targeting MHC molecules. This approach is effective in some animal models of arthritis (see above) using anti-Ia mAbs. An alternative approach is to blockade the MHC using non-immunogenic peptides.

Conclusions

Immunotherapy is likely to play an important role in the future management of autoimmune disease. The administration of mAbs to patients is safe, and capable of inducing clinical improvement. The trials reported are all open uncontrolled studies and no comparison has been made with other agents or placebo. Although responses have been
limited most patients had longstanding disease and it is likely that those with early disease will derive greater benefit. Comparison of the antibodies used is difficult as different criteria to assess response have been used and they are directed against different epitopes. Future progress, however, may depend more on learning how to use the mAbs we already have, rather than searching for a ‘magic’ target or antibody. Comparative studies of mAbs with traditional agents are urgently needed, together with uniform criteria for assessing responses. Animal studies have demonstrated that they are much more than just potent immunosuppressive and anti-inflammatory agents. Other forms of immunotherapy are still further away from the clinic, but there are exciting possibilities in the fields of MHC blockade, T cell vaccination and anti-TCR therapy.

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References


