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Leader

Immunotherapy of rheumatoid arthritis

There is now evidence that T lymphocytes, in particular the CD4+ subset, are important in the initiation and maintenance of rheumatoid inflammation.[1 2] Treatment with non-specific immunomodulating drugs, however, is often unsatisfactory owing to poor efficacy or side effects. Furthermore, although early attempts at reducing lymphocyte numbers by thoracic duct drainage,[3] lymphocytapheresis,[4] or nodal irradiation[5] were all capable of inducing a transient clinical remission, their associated toxicity or impracticality prevented widespread use. Cyclosporin A (a fungal peptide which modulates cytokine production by T cells) has been used in several trials and gives clinical improvement, but associated nephrotoxicity has limited its use.[6]

Monoclonal antibodies (mAbs) provide a novel approach to the treatment of autoimmune and inflammatory disorders by immunotherapy.[7] By targeting specific antigens on lymphocytes it is possible to destroy these cells, or modulate their function. Until recently the use of mAbs in inflammatory arthritis was confined to animal models, but a number of small open studies in humans have now been reported which show potent anti-inflammatory effects. Antigenic targets in animal models of arthritis have included CD4,[8] class II,[9] and the interleukin 2 receptor,[10] whereas in humans three main antigen targets have been considered: pan T cell antigens, CD4, and T cell activation antigens.[11] The table gives the origins of the antibodies used therapeutically in humans.

Pan T cell antigens

Antibodies against CD5 and CDw52 (the CAMPATH antigen[12]) target all mature T cells. The CD5 antigen is also present on a subset of B cells believed to play an important part in the pathogenesis of rheumatoid arthritis (RA)[13] and CDw52 is present on all lymphocytes (B and T cells) and some monocytes.[12] A total of 95 patients have now been treated with CD5 plus, a murine CD5 antibody linked to the ricin A chain (a potent plant toxin). In a phase II study 41 of 79 patients improved by more than 50% in four of six clinical parameters one month after the start of treatment. Seventeen showed an improvement by six months and six by ten months after the start of treatment.[14] Preliminary data from this study suggest 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).[15] The part played by the ricin A chain in the clinical response is uncertain as no data are available on the unconjugated antibody. CAMPATH-1H is the only humanised mAb used clinically so far. It has been given to one patient with RA[16] in whom clinical improvement was obtained for 12 weeks. Currently an open study is underway in Cambridge and an international phase I trial is due to begin shortly. Humanisation of antibodies should reduce the antiglobulin response often seen as a result of treatment with mAbs.

T cell helper antigen CD4

Five murine and one chimeric CD4 mAb have been used in the treatment of RA (table). By limiting their effect to the CD4 subset, they should be less immunosuppressive than the aforementioned mAbs although maintaining therapeutic efficacy. Herzog and coworkers reported the first use of murine CD4 mAbs in seven patients with RA and one with psoriatic arthritis.[17 18] Within one week of beginning treatment there was an average of 70% improvement in the Ritchie articular index and a 59% decrease in morning stiffness. The improvement was maintained for up to five months (mean 11 weeks) although no change in the erythrocyte sedimentation rate, C reactive protein, or rheumatoid factor levels occurred during or after treatment. Subsequently four murine mAbs have been used in small open uncontrolled trials (table).[19-24] Improvements in measures such as the Ritchie articular index and joint score have been seen in many patients, lasting up to 12 months in some. Conversely, the erythrocyte sedimentation rate, C reactive protein, or rheumatoid factor titre usually remain unchanged.

T cell activation antigens

Activation antigens are present on T cells following stimulation by an antigen and should therefore include the self reactive clones in autoimmune disease. By further focusing the immune attack, antibodies against them ought to result in less immunosuppression than that seen with CD4 mAbs. CAMPATH-6, a rat antibody directed against the interleukin 2 receptor (CD25), produced a three month improvement in two of three patients treated.[25] Conversely murine and chimeric mAbs against CD7, an activation antigen of unknown function, did not lead to major improvements in 16 patients treated.[26 27]

Complications of treatment with antibodies

Rodent antibodies usually produce an antiglobulin response in humans,[28] and the trials described here 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.[19 20 29] Genetic engineering has led to the development of recombinant antibodies, either chimeric (rodent variable region in association with a human constant region), or fully humanised (in which only the binding site of the mAb remains foreign).[30] Two trials of a chimeric CD4 mAb and one of a CD7 mAb have been reported.[27 31 32] In an open study, 33 patients with RA were treated with a chimeric CD4 mAb (table).[32] Significant improvements in the Ritchie articular index and the number of swollen joints were observed at one and three months, although the C reactive protein and rheumatoid factor levels did not change. Moreland *et al* reported 25 patients treated with the same chimeric CD4 mAb and methotrexate, of whom eight were improved at six months after the start of treatment.[31] As anticipated the incidence of an antiglobulin response was lower following the use of the chimeric CD4 mAb compared with the murine CD4 mAb.[33] No antiglobulin response was observed in the patient treated with CAMPATH-1H.[16]

Although potently immunosuppressive, mAbs have not so far been associated with a high incidence of infection when used alone. When they do occur, infections are usually of viral origin and are seen in association with concurrent immunosuppressive treatment.[34 35]

There is an increased incidence of malignancy in patients receiving OKT3 (a CD3 mAb) for the treatment of transplant rejection. Again, this appears to relate to the overall degree of immunosuppression rather than treatment with antibodies alone.[36] Nonetheless, this factor must not be forgotten, particularly in younger patients.

Prospects for the future

These studies have shown that mAbs can be safely used in the treatment of RA. Therapeutic benefit has generally been of short duration, but most studies have concentrated on patients with refractory, longstanding disease. The phase II CD5 plus study suggests that superior results may be obtained in patients with earlier disease. It is now important to concentrate on the most appropriate ways to use mAbs. Animal studies have shown that they are much more than just potent immunosuppressive and anti-inflammatory agents. Thus donor specific transplantation tolerance can be achieved across major histocompatibility barriers, even in sensitised animals[37]; however, this requires much higher doses of antibody than are needed to suppress a primary skin graft rejection reaction. Similarly, achieving control of the self reactive T cell population in patients with RA is likely to require much higher doses of antibody than the anti-inflammatory regimens used so far. Alternatively, combinations of mAbs may be necessary to alter the natural history of the disease, as reported in a patient with vasculitis.[38]

Monoclonal antibodies used in the treatment of patients with rheumatoid arthritis

Target	*Source*	*Isotype*	*Designation*	*Reference*
CD4	Mouse	IgG_{2a}	V1T4	17, 18
CD4	Mouse	IgG_1	16H5	19
CD4	Mouse	IgG_{2a}	M-T151	18, 20
CD4	Mouse	IgG_1	B-F5	21-23
CD4	Mouse	IgG_{2a}	BL4	24
CD4	Human/mouse Chimeric	$hIgG_1$	cM-T412	31-33
CD5	Mouse	IgG_1*	CD5 plus	14, 15
CD7	Mouse	IgG_{2a}	RFT2	26
CD7	Human/mouse Chimeric	$hIgG_1$	SDZ CHH-380	27
CD25 (IL2-R)	Rat	IgG_{2b}	CAMPATH-6	25
CDw52	Humanised rat	$hIgG_1$	CAMPATH-1H	16

*Conjugated to the ricin A chain.

Other potential targets for mAbs include monocytes or their cytokine products, such as tumour necrosis factor α, interleukin 1, or interleukin 6. Molecules important in the interaction between leucocytes and endothelium such as selectins and integrins are other possibilities, although antibodies against these structures are unlikely to influence long term disease progression. In animals with experimental allergic encephalomyelitis (a model for multiple sclerosis) only a small number of T cell clones inflict damage on the central nervous system.[39] If a similar oligoclonality is found in patients with RA, treatment with antibodies could be refined further; so far, however, most patients studied have had a polyclonal T cell response.

Alternatives to treatment with mAbs include T cell vaccination either with intact (though inactivated) T cells or with peptides derived from T cell receptors. The idea is to induce specific immunity to the T cells responsible for the disease,[40] possibly invoking idiotypic networks. Preliminary data suggest that this approach may result in the modulation of disease activity,[41] but there are major problems to be overcome if this technique is to become clinically useful.[40]

Immunotoxins are a means of directly delivering toxic molecules to target cells. The CD5 mAb ricin conjugate has already been discussed. The interleukin 2 receptor has been targeted using a genetically engineered fusion protein consisting of the toxic component of diphtheria toxin and interleukin 2. Thus the toxin is delivered directly to activated T cells bearing the interleukin 2 receptor. Thirteen patients have been treated in an open uncontrolled trial, most with transient benefit.[42]

Conclusions

Immunotherapy is likely to play an important part in the future management of RA. Monoclonal antibodies can be given safely to patients with RA and are capable of inducing clinical improvement. The reported trials are all open, uncontrolled studies and no comparison has been made with other agents or a placebo. Although responses have been limited most patients had longstanding disease and it is likely that those with early disease will derive greater benefit. A comparison of the antibodies used is difficult as different criteria have been used to assess the response. Future progress, however, may depend more on learning how to use the antibodies we already have rather than searching for a 'magic' target or antibody. Comparative studies of mAbs with traditional treatments are urgently needed, together with uniform criteria for assessing response.

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