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Clinical opinions

Experimental medicines in multiple sclerosis and compassionate use

JS Kelly

Editor, Clinical Section, *Journal of the Royal College of Physicians of Edinburgh, Edinburgh, UK*

TITLE Alemtuzumab vs. Interferon beta-1a in early multiple sclerosis

AUTHORS Coles AJ, Compston DAS, Selmaj KW et al.

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Correspondence to JS Kelly, Division of Neuroscience, University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK

tel. +44 (0)131 444 0512
e-mail J.S.Kelly@ed.ac.uk

SUMMARY

Although multiple sclerosis usually begins as a relapsing-remitting disease, for most patients it appears sooner or later to be a progressive neurological disorder. The relapsing phases are usually heralded by focal bursts of inflammation in the white matter of the spinal cord and brain, while during the progressive phase there is a slow, relentless axonal and neuronal loss. The focal bursts of inflammation not only result in demyelination, incomplete remyelination and gliosis but are believed to sensitise surviving axons to additional insults at a later date, and in essence shorten their life span. Thus although it is believed that the main cause of loss of mobility is the progressive disease, the main thrust of treatment is to abort or reduce the inflammatory relapses and, indirectly, disease progression. In any event, the only active drugs available at present are directed against the relapses. Although these drugs, interferons and glatiramer acetate, are strikingly effective in some patients, they at best reduce the relapse rate by only one third. Hereby lies the motivation of a number of trialists in this field to test compounds that are known to limit the activity of the immune system yet are certain to have serious or even extreme side effects.

In this paper Coles et al. report on a randomised, blinded phase 2 trial on 334 previously untreated patients with

early relapsing-remitting multiple sclerosis with a disease duration of three years or less. The 111 patients in one arm of the trial received subcutaneous injections of beta-1 interferon three times per week, and the 223 in the other an annual intravenous cycle of three or five days of alemtuzumab (12 or 24 mg daily) for 36 months. The trial of alemtuzumab was suspended in September 2005 after three patients developed immune thrombocytopenic purpura, one of whom died. Three more patients with this adverse reaction were identified later in 2005 and 2006 after the trial ended. One patient in the beta-1 interferon group developed asymptomatic, chronic immune thrombocytopenic purpura.

The results, however, were dramatic. As compared with beta-1 interferon, alemtuzumab reduced the risk of sustained disability or relapse by 71% and 74% respectively, and these effects were independent of dose. The number of patients needing to be treated with alemtuzumab instead of beta-1 interferon during a three-year period to avoid a disability event was 5.8 and, rather strikingly, 3.5 to avoid a relapse. These differences were mirrored by a significant difference in changes in brain volume between the two groups measured by T1-weighted magnetic resonance imaging at 12 and 36 months, with a reduction of 0.2% in brain volume in the patients receiving beta-1 interferon and an increase of 0.9% in those treated with alemtuzumab. The

reduction in brain volume in patients receiving beta-1 interferon is consistent with similar findings in earlier studies. The authors attribute the novel finding of an increase in volume to the secretion of neurotrophins by regenerated lymphocytes following ablation by alemtuzumab, and support this by referencing an abstract of their own.

Serious adverse effects in the alemtuzumab group greatly exceeded those in the beta-1 interferon group and included autoimmunity, in particular thyroid disorders (23% vs 3%), immune thrombocytopenia (3% vs 1%) and infections (66% vs 47%). However, the trial was not powered to pick up differences in less serious side effects. The authors concluded that 'in patients with early relapsing-remitting multiple sclerosis, alemtuzumab was more effective than beta-1 interferon but was associated with autoimmunity...'

OPINION

Although this study is labelled a phase 2 trial, a better title would be a proof-of-concept trial. The study shows beyond doubt that intensive immunosuppression can reduce the number of new inflammatory lesions and the rate of relapse in patients with recent onset multiple sclerosis, and the possible value of adopting a very aggressive therapeutic approach at the beginning of the disease process when the extent of the diseases is not obvious to the patient and the level of disability is either mild or absent. In his review of the paper, Stephen Hauser¹ draws a parallel with the current approach to what are now standard models of cancer therapy in which intensive therapy is followed by a more relaxed approach to maintenance. Although the outcome of the trial is promising and the undoubted toxicity of alemtuzumab makes its routine use unlikely, the possibility remains that the early use of alemtuzumab may have a long-term benefit by halting the relentless advance of the progressive phase of the disease. Indeed, there are data from an earlier study² to suggest that, following lymphocyte depletion by alemtuzumab, homeostatic mechanisms appear to drive the reconstitution of the lymphocytic pool and may reduce the need for further bouts of treatment.

As highlighted by Hauser, this is not the first attempt to use immunosuppressants in multiple sclerosis to limit the inflammatory phase of the disease. Mitoxantrone was approved by the FDA in 2000; however, the risk of leukaemia and cardiomyopathy has limited its use. Of course, the trial also raises worries about the efficacy of beta-1 interferon. In their comprehensive review of the multiple sclerosis literature, Compston and Coles³ draw attention to the softness of the case for using beta-1 interferon in terms of efficacy, convenience of use and adverse side effects. Indeed, in this study 41% of the patients receiving beta-1 interferon dropped out of the 36-month study due to lack of efficacy or adverse side effects, whereas only 17% of those receiving alemtuzumab failed to complete the study.

This study is only one of many that herald a new approach to multiple sclerosis for neurologists and individual patients. Some will see efficacy as the overriding issue, whereas others will focus on safety and the acceptability of side effects. It could be that patients will take the lead and seek out new therapies offering greater efficacy, and may take a more sanguine view of the risk–benefit balance. The NHS website⁴ under the heading 'choices' suggests that natalizumab may reduce the number of relapses by two thirds and slow the progression of the disease by half. Although the account stresses the side effects, including progressive multimodal leukoencephalopathy and the possibility of problems with vision, speech and mobility, it is clear that a selected group is receiving this new treatment. In spite of similar warnings in the US, more than 20,000 patients have received natalizumab.

It is worth noting that in a small study⁵ in the US it has been shown that 82% of the patients with a possible diagnosis of multiple sclerosis had gathered information about their condition and treatment online before their first appointment, but only 36% discussed their finding with their physician. Although similar results have been obtained in a number of studies related to other conditions, they are all very small and centred on clinics in the US. However, it could be that in the UK a simple question about the patients' prior knowledge from the internet may be a good lead-in to a discussion of the benefits of more efficacious treatments and the downside of the serious side effects for a few individuals.

Ross⁶ has drawn attention to the work of Richard Bedlack⁷ and others who have commented on the number of motor neurone disease patients seeking access to experimental drugs and, indeed, obtaining drugs from pharmaceutical companies under schemes known as 'expanded access' or 'compassionate use'. However, Ross quotes from several directors of leading companies who highlight reasons why this practice is declining and may be of disadvantage to the company since it can highlight adverse effects in severely ill patients. Bedlack concludes his paper: 'We should refrain from off-label prescribing of unproven therapies. Most importantly, we need to educate patients on how to distinguish myth from reality as it applies to the complex world of clinical research.'⁷ Despite this, Ross identifies websites where patients receiving new drugs either in or out of trials share their experiences and quotes from a director who favours compassionate use.

The publication of this careful paper by Coles and colleagues and the accompanying editorial by Hauser in the *New England Medical Journal* was greeted in the media by considerable hyperbole. Although on careful reading some of these accounts can be described as responsible, the headlines are by and large outrageous: "'Landmark drug' raises hope of reversing multiple sclerosis in early stages of the disease'.

Addendum: A separate study has recently been published in which 17 of 21 patients received autologous non-myeloablative haemopoietic stem cell transplants following conditioning with cyclophosphamide and a single 20-mg dose of alemtuzumab.⁸ Two of these patients developed grade IV thrombocytopenia at seven and

14 months after transplantation. Rabbit antithymocyte globulin was substituted for alemtuzumab for the last four patients following the adverse report published by the FDA. Although five patients needed a further round of immunosuppression, all 21 patients were free from progression at 37 months and 16 were free from relapses.

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Tailoring treatment with targeted therapies for advanced colorectal cancer

LK Dawson

Consultant, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

TITLE 1 KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab

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AUTHORS 1 Lièvre A, Bachet J-B, Boige V et al.

Correspondence to LK Dawson, Edinburgh Cancer Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK

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TITLE 2 Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer

tel. +44 (0)131 537 3916

AUTHORS 2 Amado RG, Wolf M, Peeters M et al.

e-mail

lesley.dawson@luht.scot.nhs.uk

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DECLARATION OF INTERESTS The author is the local principal investigator for the COIN and PICCOLO studies and has received funding and an educational grant from Merck.

SUMMARY

These two complementary papers reflect the emergence of data over the course of 2008 that have changed the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies. Two monoclonal antibodies directed at the epidermal growth factor receptor are currently licensed for the treatment of advanced colorectal cancer: cetuximab and panitumumab.

89 patients and analysed for KRAS mutational status. The patients' clinical responses to cetuximab were assessed on serial computed tomography (CT) scans using internationally recognised response criteria. It was shown that there was a significant association between KRAS mutations and response: none of 24 patients (0%) with KRAS mutations responded to cetuximab, while 25 of 65 patients (39%) who had wild-type (non-mutated) KRAS responded. Pooling the data from the previous study showed similar results (0% vs 44%). This response also translated into improved survival.

Lièvre et al. investigated the prognostic role of KRAS (Kirsten rat sarcoma viral oncogene, which codes for a signalling protein in the EGFR pathway) mutations in the treatment of patients with cetuximab and chemotherapy for advanced colorectal cancer. This was a retrospective study to validate previous work which had suggested that KRAS status could predict response to cetuximab. Mutations in KRAS status were hypothesised to be associated with poorer outcomes. DNA was extracted from frozen or paraffin-embedded colorectal cancer tissue samples from

Amado et al. reported a retrospective analysis of the KRAS status of 427 patients who had been treated in a phase three clinical trial comparing panitumumab (a fully humanised monoclonal anti-EGFR antibody) with best supportive care. This was a more homogenous group of patients compared with the study above. Seven potential KRAS mutations were assessed. Again, there was a significant association between KRAS mutations and response rate; none of the patients with KRAS mutations