Alemtuzumab in Multiple Sclerosis

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ABSTRACT

Alemtuzumab is a humanised monoclonal antibody directed against CD52. After a single pulse of therapy, it causes an initial depletion of lymphocytes; the resulting homeostatic reconstitution leads to prolonged alteration of the lymphocyte repertoire. In a phase 2 trial, two annual cycles of alemtuzumab (eight days of infusion in total) reduced relapse rate, reduced the risk of sustained disability accumulation and improved disability measures in early relapsing-remitting multiple sclerosis when compared to active treatment (interferon beta-1a), over at least five years. The major safety concern of alemtuzumab as a therapeutic agent is the late emergence of secondary autoimmunity which has been observed in up to 25% of treated patients, and may be predicted by baseline serum IL-21 levels. Phase 3 trials of alemtuzumab in multiple sclerosis will report in 2012.

Key words: Multiple sclerosis, Monoclonal antibodies, alemtuzumab, anti-CD52

Introduction

The possibility to harness antibodies for therapeutic use only emerged after Kohler and Milstein identified a method of producing antibodies of a given specificity by fusing an antibody-producing cell with a myeloma cell (1). In the early 1980s, Herman Waldmann and Geoff Hale utilised this technology to generate a rat monoclonal antibody that would lyse human lymphocytes, and so, treat lymphocytic malignancies. They developed the Cambridge Pathology-1, or Campath-1, series of antibodies. These were amongst the first monoclonals to be ‘humanised’ by Greg Winter Winter’s group (2), and hence, Campath-1H, now called alemtuzumab, was born.

At present, alemtuzumab is only licensed for the treatment of fludarabine-resistant chronic lymphocytic leukaemia (CLL), but it has been used with success in a variety of autoimmune diseases (3-7), as well as in renal transplantation (8) and non-myeloablative conditioning prior to stem cell therapy (9).

Extrapolating from its use in leukaemias and other autoimmune conditions, the initial rationale for use of alemtuzumab in multiple sclerosis, in 1991, was to induce a state of lymphodepletion and halt autoimmune-driven mechanisms of injury. However, the observation that patients treated using alemtuzumab had few of the opportunistic infections associated with immunodeficiency, and the emergence of secondary autoimmunity seen in 30% of patients, suggest that immune function has been modulated rather than suppressed. Clinical experience with alemtuzumab in multiple sclerosis suggests that its promising efficacy is maximal when given to patients with early active relapsing-remitting disease.
This review is based on our open-label studies of alemtuzumab in multiple sclerosis and the multicentre rater-blinded phase 2, controlled, trial called “CAMMS223” (10).

The Biology of Alemtuzumab

Alemtuzumab targets CD52, a glycoprotein present on all T- and B-lymphocytes, monocytes and eosinophils, but importantly not on haematological precursors (11). A single pulse of alemtuzumab (five-day cycle of treatment, either 12 or 24mg/day) results in a profound and prolonged T-cell lymphopaenia as well as transient depletion of B-cells and monocytes (12). The mechanisms of lymphodepletion have been studied in a transgenic mouse model expressing human CD52 (13). Treatment with alemtuzumab in the CD52 transgenic mouse following complement depletion had no influence on lymphocyte depletion. In contrast, treatment following removal of NK cells or neutrophils reduced the impact of alemtuzumab treatment. This model has thus suggested that lymphocyte depletion by alemtuzumab is predominantly antibody-dependent cytotoxicity.

Following lymphodepletion, homeostatic mechanisms drive the reconstitution of lymphocytes. In the first six months after treatment, the reconstitution pool is dominated by memory cells (in particular CD4+ CD25 high FoxP3+ T-cells), regulatory T-cells, and bone marrow-derived B-cells (12,14). There is subsequently a return towards a normal distribution of T-cell subsets within the reconstituting lymphocyte pool, with increasing naive T-cells. Cell type proportions however do not return to baseline. CD4+ T-cells are particularly slow to reconstitute, remaining depleted for a median of 5 years following treatment (15). Hence, the postulated effect of treatment with alemtuzumab is a profound and sustained alteration in the immune cell pool following induced lymphopaenia.

One manifestation of this altered lymphocyte repertoire is the in vitro finding that peripheral lymphocytes reconstituted after alemtuzumab are able to secrete neurotrophins such as brain-derived neurotrophic factor (BDNF), if stimulated by myelin basic protein. In turn, BDNF in vitro promotes neuronal survival, axonal growth, and oligodendrocyte maturation and survival. This release of neurotrophins may underlie the restoration of brain tissue post-alemtuzumab (16).

Efficacy of Alemtuzumab in Multiple Sclerosis

Open-label experience of alemtuzumab treatment of multiple sclerosis.

Alemtuzumab as an experimental therapy in multiple sclerosis was first used in a cohort of 36 patients with secondary progressive multiple sclerosis, with mean disease duration of 11.2 years (SD 6.1) and mean Expanded Disability Status Scale (EDSS) score of 5.8 (range 3.5–7.0). Recruited patients had a pre-treatment annual relapse rate of 0.7 with worsening of disability of at least one point on EDSS in the preceding year. Annual relapse rate following treatment fell from 0.7 to 0.02 (97% reduction). In addition, new MRI lesion formation was reduced by 90%, and at 7-year follow-up, the cerebral lesion volume on imaging had not significantly changed (23). Nevertheless, progressive deterioration and accumulation of disability continued to be observed amongst these participants, with a mean rate of EDSS score increase of 0.2 points per patient per annum (15,17). These patients also appeared to have greater cerebral atrophy at 7-year follow-up imaging.

The second group of patients to be treated with alemtuzumab consisted of an open-labelled study of 22 active relapsing-remitting multiple sclerosis patients with features of aggressive disease, namely a high early relapse rate or failure of licensed treatment (interferon-beta) to control disease. Mean disease duration in this group was 2.7 years (SD 2.9) and mean EDSS was 4.8 (range 1.0–7.5). The pre-alemtuzumab annual relapse rate was 2.2 per patient. Similar to the initial group, this cohort also experienced a reduction in annual relapse rate, from 2.2 to 0.14 (94% reduction). However, in contrast to the secondary progressive group, the relapsing-remitting multiple sclerosis cohort showed an improvement also in their disability score, with a sustained EDSS reduction of 1.2 points at 24 months from alemtuzumab treatment.

Taken together, these two clinical experiences suggested that there is an early “window of therapeutic opportunity” in multiple sclerosis, during which anti-inflammatory treatments can alter the long-term risk of disability accumulation; but once in the secondary progressive phase, the progression of multiple sclerosis is not amenable to immunotherapies (15).

Randomised Controlled Studies of Alemtuzumab

CAMMS223 (ClinicalTrials.gov number NCT00050778) was a commercially sponsored, randomised, single-blinded, Phase 2 trial comparing the efficacy of alemtuzumab with current standard therapy, IFNβ-1a (Rebif) (34). A total of 334 patients were recruited at 49 centres across Europe and the US, with recruitment starting in 2003 and extending over a three-year period. Based on the hypothesis of “window of therapeutic opportunity”, eligible patients had a diagnosis of relapsing-remitting multiple sclerosis with disease onset within the previous 36 months and with an EDSS score of 3 or less. Active relapsing-remitting multiple sclerosis was confirmed by clinical and radiological measures (at least two relapses in the preceding two years and at least one gadolinium-enhancing lesion on MRI). Patients who had previously received DMT or had a history of autoimmunity were excluded from trial. Patients were randomized to treatment with IFNβ-1a (44 micrograms subcutaneously three-times weekly, n=111) or annual cycles of alemtuzumab at one of two doses (12 mg daily, n=112, or 24 mg daily, n=110). In comparison with IFNβ-1a, alemtuzumab significantly reduced the rate of relapse in relapsing-remitting multiple sclerosis. Annual relapse rate was 0.36 in the IFNβ-1a group compared to 0.1 in alemtuzumab-treated patients (74% reduction). The risk of sustained accumulation of disability was also reduced in alemtuzumab group by 71%. Mean EDSS improved by 0.39 points in the alemtuzumab group, compared to a worsening of 0.38 point in the IFNβ-1a group, representing a significant improvement of disability with alemtuzumab (p<0.001) (10).
Post-hoc and subset analyses of CAMMS223 outcomes have further examined the trial data with the aim of determining whether certain patient-specific characteristics exert an influence on the disability and relapse outcomes of alemtuzumab (18). Outcomes were analysed for patient subgroups based on demographic factors, baseline MRI-T1 brain volume and MRI-T2 lesion volume, disease duration, number of relapses within two years, and EDSS. All patient subgroups showed evidence of beneficial effects of alemtuzumab with no subgroup consistently responding better than others.

An extension study of the CAMMS223 trial (Coles 2011, Neurology, in press) has shown that two annual cycles of alemtuzumab, and no further therapy, continues to have durable efficacy, compared to the active therapy interferon-beta, over at least five years.

Two phase 3 trials of alemtuzumab have yet to report. The randomised, single-blinded CAMMS323 trial (CAREMS-I) compares alemtuzumab with Rebif in over 580 treatment-naive patients with early-active multiple sclerosis. The second trial, CAMMS324 (CAREMS-II), compares alemtuzumab with Rebif in over 800 relapsing-remitting multiple sclerosis patients, who have relapsed at least once while on standard disease-modifying therapy.

Safety of Alemtuzumab in Multiple Sclerosis

Infusion-associated symptoms

Similar to other cell-depleting antibodies, the first dose of alemtuzumab is associated with cytokine induction and release resulting in an infusion reaction. Patients may experience influenza-like symptoms, fever, rash, and headache mediated by increased serum levels of IL-6, TNFα and IFNγ. Less frequently, a transient re-emergence of previous multiple sclerosis symptoms may be seen, possibly due to conduction block at sites of previous demyelination (19). Pre-treatment with corticosteroids and anti-histamines reduces these symptoms.

Autoimmunity

The principal adverse effect of alemtuzumab is secondary autoimmunity arising months to years after pulsed exposure, a recognised complication of lymphopaenia reconstitution (20). The commonest target organ involved is the thyroid gland, with up to 30% of alemtuzumab-treated patients affected, usually manifesting as hyperthyroidism (Graves’ disease). Biochemical screening of thyroid dysfunction is thus performed regularly in the context of alemtuzumab treatment. 3% of patients in CAMMS223 developed immune thrombocytopenic purpura (ITP); a fatality due to intracranial haemorrhage in the index case led to the voluntary suspension of alemtuzumab dosing in the CAMMS223 trial. Subsequently, a risk management plan was developed that, in the current Phase 3 trials, requires patients to undergo monthly blood investigations and encourages early recognition of symptoms. All subsequent cases of ITP were treated successfully. Other less common auto-immune conditions have occurred following alemtuzumab, including three cases of anti-glomerular basement membrane disease (Goodpasture’s syndrome), autoimmune neutropaenia and autoimmune haemolytic anaemia (15).

This occurrence of secondary autoimmunity, attributed to altered lymphocyte reconstitution, was found to arise in patients with greater T-cell apoptosis and cell cycling after alemtuzumab exposure. This increased T-cell turnover is driven by high circulating levels of the cytokine IL-21. On comparing the pre-treatment levels of serum IL-21, those patients who developed secondary autoimmunity had a more than two-fold greater level of IL-21 than those patients who did not express post-alemtuzumab autoimmunity. Thus, serum IL-21 may have a role in identifying patients at risk prior to treatment, enabling pre-treatment counselling and focused surveillance (21).

Infections

In the CAMMS223 trial, mild-to-moderate infections, predominantly respiratory tract infections, were reported more frequently after alemtuzumab (10). Eight other cases of infections potentially attributable to immune-suppression have been reported, including three cases of shingles, and one case each of pyogenic granuloma, Listeria meningitis, chicken pox and measles. To date, serious opportunistic infections such as progressive multifocal leukoencephalopathy, cytomegalovirus and pneumocystis jirovecii, have not been observed.

Malignancy

A significant risk of neoplasia following alemtuzumab has not, as yet, been observed. The only reported neoplasm which is likely to have been related to alemtuzumab is one case of fatal Epstein-Barr virus-negative Burkitt’s lymphoma, which was reported in a patient two years following the third cycle of treatment in CAMMS223 trial.

Anti-Alemtuzumab Antibodies

Surprisingly perhaps, given that it is a humanised antibody, antibodies against alemtuzumab develop with significant frequency; for instance, a month after the second annual pulse of alemtuzumab, some 70% of patients have detectable antibodies. This is not usually a clinical problem as the next cycle of alemtuzumab is likely to be given at least 12 months later, by which time the anti-alemtuzumab concentration has usually fallen to undetectable levels in those in whom it was positive. But anti-alemtuzumab antibodies may remain elevated for prolonged periods after repeated cycles of therapy. Anticipating that such antibodies might neutralise the efficacy of alemtuzumab at some point, we tested a novel strategy to reduce the immunogenicity of alemtuzumab and other biologicals. In a trial of just 20 patients, a replica of alemtuzumab, mutated at one amino acid to prevent it binding to CD52, was given at high concentration to induce “high-zone tolerance”; this reduced the number of patients who developed antibodies to subsequent pulses of alemtuzumab (22).
The Future of Alemtuzumab

Alemtuzumab is emerging as an extremely promising treatment option in multiple sclerosis. In early, relapsing-remitting multiple sclerosis, it has the potential to prevent or delay disability over many years. Concern about its use however remains in view of significant adverse effects, in particular secondary autoimmune disease. The possibility that serum IL-21 might predict the risk of developing secondary autoimmunity is an exciting and active area of research. In the meantime, we are focused on developing pragmatic monitoring schedules that will identify thyroid dysfunction or a falling platelet count before they cause symptoms and to allow effective therapy. It is conceivable that other adverse events, occurring at low frequency, are yet to emerge from the phase 3 programme. The efficacy of two annual pulses of alemtuzumab is clear, at least up to five years. But how more prolonged this effect is, and whether further cycles should be given, and at what intervals, is being explored in the “Extension Trial” of the alemtuzumab programme.

The sponsors of alemtuzumab, Genxyme (a Sanofi company), anticipate submitting alemtuzumab for licensing in multiple sclerosis in 2012.

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References