

## Occasional viewpoint

# Stem cell transplantation for inflammatory bowel disease: practical and ethical issues

There is growing interest in the use of autologous stem cell transplantation for a number of autoimmune diseases, including systemic sclerosis, rheumatoid arthritis, and multiple sclerosis.<sup>1–7</sup> Recent case reports have raised the possibility that indications might be extended to inflammatory bowel disease.<sup>8,9</sup> However, this would raise practical and ethical issues not encountered in other conditions. Inflammatory bowel disease activity involves a delicate and unpredictable balance between tolerance and immune reactivity to luminal factors that makes the outcome of stem cell transplantation difficult to predict. Ethically, stem cell transplantation is more acceptable in some cases of systemic sclerosis where life expectancy is reduced or in multiple sclerosis where, additionally, there are few alternative effective treatments. Neither of these principles apply to inflammatory bowel disease.

### Background

Intensive myelosuppressive or myeloablative chemotherapy followed by transplantation of stem cells derived directly from the bone marrow or from peripheral blood after suitable conditioning, has revolutionised the management of haematological malignancy and haemoglobinopathies. Because these manoeuvres cause significant and prolonged alterations in the body's immune system and function, stem cell transplantation has, in recent years, been used for severe cases of diseases that are believed to have an autoimmune basis. These diseases have included systemic sclerosis and multiple sclerosis but also rheumatoid arthritis, systemic lupus erythematosus, vasculitis, juvenile rheumatoid arthritis, and myasthenia gravis.<sup>1–7</sup>

Stem cell transplantation can either be allogeneic (from a donor, usually a HLA matched sibling) or autologous<sup>10,11</sup> (harvested from the individual undergoing treatment with later reinfusion). Syngeneic transplantation (from an identical twin) is also possible. Because of the higher mortality of allogeneic transplantation, most human experience is with autologous transplants. Data are still uncontrolled but there is growing evidence of benefit in the main conditions that have been treated (including systemic sclerosis and multiple sclerosis).<sup>12–17</sup> Hitherto, selection for treatment has been guided by the principle that "only diseases severe enough to have an increased risk of major organ damage or mortality should be considered".<sup>18</sup> With growing experience, there is a move to making prevention of major organ damage and amelioration of impaired quality of life criteria for transplantation.

### Possible benefits of stem cell transplantation in Crohn's disease

#### ALLOGENEIC TRANSPLANTATION

Crohn's disease is sufficiently common that some patients undergoing allogeneic transplantation for haematological malignancy will also have Crohn's disease. Recently, the clinical course of six such patients has been reported.<sup>8</sup> One patient with inactive Crohn's disease remained inactive for over 15 years despite discontinuation of immunosuppressive therapy. Of five patients with active Crohn's disease before transplantation, three became and remained

inactive for 6–10 years after transplantation, despite discontinuation of immunosuppressive treatment. Two of these patients had objective evidence of active Crohn's disease (one with an ileo-colic fistula) at the time of transplantation while in the third the evidence for activity was presumptive (and not very strong). Post-transplantation regression of disease was established in one individual by colonoscopy and in the other two on the basis of absence of symptoms.

Two patients fared less well. One developed recurrent Crohn's disease with a perirectal abscess and fistula formation 545 days after transplantation and required a neoterminal ileal resection on day 640 (he had stopped immunosuppression at six months). Following resection his Crohn's disease remained asymptomatic (but on prednisolone). He committed suicide 5.8 years after transplantation (not related to Crohn's disease). A sixth patient died from septic shock 97 days after transplantation and the effect of this manoeuvre on his Crohn's disease was not evaluable. Also, there was a case report of improvement in Crohn's disease following allogeneic transplantation but the follow up was relatively short.<sup>19</sup>

#### AUTOLOGOUS TRANSPLANTATION

A single case of regression of Crohn's disease following autologous stem cell transplantation has been reported in full.<sup>9</sup> A nine year old male developed cramps and diarrhoea and was diagnosed with Crohn's disease four years later. For seven years he required active treatment of his Crohn's disease, including drainage of a perirectal abscess when 19 and a right hemicolectomy. He developed non-Hodgkins lymphoma aged 20 and underwent autologous stem cell transplantation. In the seven years following transplantation there was no clinical or laboratory evidence of recurrence of either non-Hodgkins lymphoma or Crohn's disease. In addition, a case of Crohn's disease and a case of ulcerative colitis have been described in an abstract. The patient with Crohn's disease had a diffuse pan colitis before transplantation and was asymptomatic but had inflammation at endoscopy (three years later). The patient with colitis had mild left sided inflammation before transplantation and was asymptomatic off medication two years after transplantation.<sup>20</sup>

#### POSSIBLE BENEFITS OF STEM CELL TRANSPLANTATION IN ULCERATIVE COLITIS

Two patients with a long history of psoriasis and ulcerative colitis underwent an allogeneic stem cell transplantation for leukaemia. The colitis, psoriasis, and leukaemia remained in remission for four years following transplantation.<sup>18</sup>

#### POSSIBLE HAZARDS OF STEM CELL TRANSPLANTATION IN INFLAMMATORY BOWEL DISEASE

As well as the intrinsic dangers of stem cell transplantation, which include mucositis, there are also some data suggest-

**Abbreviations used in this paper:** GCSF, granulocyte colony stimulating factor.

ing that stem cell transplantation may either worsen or at least not prevent inflammatory bowel disease in some patients. Three patients have been reported to develop ulcerative colitis or colonic ulceration after allogeneic stem cell transplantation.<sup>21-23</sup> All of the cases of colitis were atypical of ulcerative colitis and an element of graft versus host disease may have been involved. In some animal models, stem cell transplantation has provoked a type of colitis<sup>24</sup> associated with graft versus host disease.

#### ASSESSMENT OF THE EVIDENCE SO FAR

Some of these case reports suggest that stem cell transplantation may be of value in inflammatory bowel disease. However, none of the evidence available even approaches a level of proof. All but one of the cases had allogeneic transplantation whereas only autologous transplantation, with its lower (but still substantial) mortality, is currently regarded as ethical in autoimmune disease. Thus the evidence for the form of transplantation one might want to investigate in Crohn's disease is limited at present. Any move in this area would be essentially pragmatic as a clear mechanism of action that might justify intervention on theoretical grounds has not emerged. Equally, the pathogenesis of inflammatory bowel disease is sufficiently obscure that one cannot discount the possibility that it could be a different disease when it presents in association with malignancy.

#### SHOULD STEM CELL TRANSPLANTATION BE EVALUATED IN INFLAMMATORY BOWEL DISEASE?

Thus the evidence that exists at present does not justify use of either autologous or allogeneic transplantation<sup>25</sup> in Crohn's disease, and for any exploratory work to be conducted on an ad hoc basis would be particularly unethical. Nevertheless, it remains conceivable that stem cell transplantation could benefit patients with inflammatory bowel disease. In view of the major practical and ethical issues that would need to be resolved before its use in inflammatory bowel disease could even be considered, one way forward would be the establishment of a multidisciplinary group to evaluate if and how this treatment should be applied. Such a group might reasonably exist under the auspices of the European Register for Stem Cell Transplantation in Auto-Immune Disease, a European gastroenterology grouping. The goals of such group should be to answer the questions raised below as well as others that are generated. We believe that any such a group should set extremely high standards of conventional care that would need to be met before any patient with inflammatory bowel disease were considered for transplantation. One possible outcome might be the emergence of improved and transparent protocols of conventional care for patients with resistant inflammatory bowel disease.

We also believe that there are a number of practical and ethical issues that such a group would need to consider to establish if there would ever be circumstances under which patients failing conventional care should be considered for stem cell transplantation.

#### Practical issues

##### TRANSPLANTATION OR INTENSE IMMUNOSUPPRESSION?

Immunosuppression is a central component of inflammatory bowel disease treatment.<sup>10 11 17</sup> All gastroenterologists have seen patients in whom intense immunosuppression has been followed by major, prolonged, and sometimes permanent regression of disease. Stem cell mobilisation and conditioning for the transplant both involve intense immunosuppression to a degree that is greater than currently used in the treatment of inflammatory bowel dis-

ease. Any evaluation of stem cell transplantation in inflammatory bowel disease should assess the contribution of these periods of immunosuppression.

##### ULCERATIVE COLITIS AND/OR CROHN'S DISEASE?

There is insufficient knowledge to decide on theoretical grounds whether ulcerative colitis or Crohn's disease would be more responsive to transplantation. In practical terms, it is likely that transplantation would be difficult to conduct in patients with fulminant colitis. Such patients face the prospect of urgent surgery. For this to become necessary with the patient profoundly immunosuppressed would be unfortunate. Moreover, such patients have impaired mucosal barrier function.<sup>26 27</sup> Although profound alterations in barrier function also occur as a consequence of transplantation procedures, the double insult associated with colitis might predispose to more severe systemic sepsis. However, patients with steroid/immunosuppressive dependent colitis who relapse when such treatment is withdrawn might be plausible candidates for stem cell transplantation.

##### BONE MARROW OR PERIPHERAL STEM CELL TRANSPLANTATION?

In most quarters transplantation of stem cells mobilised to and recovered from the circulation has replaced the use of those directly harvested from the bone marrow.<sup>11</sup> This is because it is easier and cheaper, no general anaesthetic is needed, and engraftment occurs more rapidly. Peripheral stem cell transplantation requires mobilisation by single agent chemotherapy and/or use of a haemopoietic growth factor such as granulocyte colony stimulating factor (G-CSF). Use of growth factors in autoimmune disease has been associated with a temporary flare of the disease.<sup>28 29</sup> If the same occurs with inflammatory bowel disease, use of growth factors for stem cell mobilisation in inflammatory bowel disease might be sufficiently deleterious to the underlying problem to be contraindicated. If so, use of directly obtained bone marrow would be an alternative.

##### GRAFT MANIPULATION

Much of the early stem cell transplantation for autoimmune disease involved purging to deplete the graft of T cells by at least two logs.<sup>30</sup> This was done both on theoretical grounds and because animal data suggested this could increase success rates.<sup>4</sup> Purging is done by positive selection of CD34 cells with or without a second negative purging step to remove T and/or B cells. However, the current data on 145 patients in the autoimmune transplant programme does not suggest that such purging has a major benefit in preventing early relapse.<sup>30</sup>

##### WHICH CONDITIONING REGIMEN?

Prior to transplantation for autoimmune disease it is necessary to suppress the existing autoaggressive immune system. Four regimens (all traditionally used when transplantation is deployed in the treatment of haematological malignancy, involving intensive treatment and/or antithymocyte globulin and/or total body irradiation) have become standard for transplantation for autoimmune disease.<sup>18</sup>

##### WHICH PATIENTS?

For any new treatment, particularly one that is dangerous, a natural instinct is to reserve it for those who have failed existing treatments. In many diseases this is probably counter productive because involvement of secondary (non-immune) mechanisms may obscure benefits. Selection of treatment failures in inflammatory bowel disease may however not be illogical. Secondary problems (for

example fibrosis or sepsis) are relatively easy to identify and active inflammatory bowel disease continues to have a strong immune/inflammatory component throughout its course.

### Ethical issues

#### TRADE OFFS

Inflammatory bowel disease does not fulfil the criteria of clearly increased mortality to be considered for stem cell transplantation. Death from inflammatory bowel disease is extremely rare and unpredictable, and whether shortening of life expectancy can be demonstrated is controversial.<sup>31</sup> Any patient undergoing stem cell transplantation for inflammatory bowel disease would therefore be trading a risk of mortality for a possible (but unsubstantiated) improvement in morbidity. It seems likely that any programme of stem cell transplantation should be preceded by a series of theoretical time trade off evaluations in patients with severe inflammatory bowel disease. When this has been done in patients with rheumatoid arthritis, patients have registered a willingness to take substantial risks to achieve a cure.<sup>32</sup>

#### PATIENT INFORMATION

It is clear that the patient must be fully informed and must clearly want the treatment. There should be a standardised protocol that ensures that the term "fully informed" is meaningful. This is likely to include written information, a standard series of interviews with independent gastroenterologists, haematologists, and previous stem cell transplantation recipients, as well as a visit to a transplant unit.

#### PATIENT PROTECTION

##### (a) From doctors

Any new treatment is a magnet for therapeutically adventurous doctors and can be a stimulus to career advancement. Moreover, transplantation units are likely to be looking for other indications because of growing uncertainty about the role of stem cell transplantation in breast cancer compared with standard chemotherapy.<sup>33</sup> For these and other reasons, any use of stem cell transplantation for inflammatory bowel disease should be conducted on a group cooperative basis and to rigorous, transparent, and widely agreed criteria for patient selection and handling.

##### (b) From themselves

Desperate people are receptive to desperate measures but are not well placed to judge whether a desperate measure is rational. Conversely, many physicians are conservative and may be unreceptive to a well considered desire by a patient to adopt a risky strategy. A major skill for physicians caring for patients with inflammatory bowel disease who consider stem cell transplantation would be to balance sound advice with patient receptiveness and to give guidance without being patronising.

#### OPTIMISATION OF PRIOR CARE

Most gastroenterologists know of patients with inflammatory bowel disease that have been regarded as untreatable but where a therapeutic intervention resulted in substantial improvement or achievement of remission. Often this occurs because a new physician simply tries a different treatment or treatment combination. While clinical trials can and should guide choice of therapy they do not establish hierarchies or combinations of treatments that are optimal for individuals. We think it would be important for patients being considered for stem cell transplantation to undergo a period of optimisation of existing therapies. This could be done to a standardised protocol, perhaps involving an n of 1 trial principle.<sup>34</sup> We envisage that this could be

coordinated by the group whose establishment this article calls for. One possible outcome would be to determine improved pathways of care for patients with severe inflammatory bowel disease that obviates the need for transplantation, at least in the vast majority of patients.

#### NEED FOR TRIAL SETTING

The practical and ethical issues surrounding transplantation for inflammatory bowel disease are so problematic that it is axiomatic that any foray into this area should be conducted from the outset in the context of a clinical trial. Maverick, go-it-alone, single centre approaches are to be discouraged. The experience of groups that have investigated the management of lymphoma or leukaemia with complex and evolving protocols should guide such a development. While it may be natural to argue that some uncontrolled experience is needed before trials are started, we believe that the particular ethical issues surrounding inflammatory bowel disease require that the interpretability of any experience with stem cell transplantation is maximised from a very early stage. Stem cell transplantation involves a number of steps and we believe it would be important to structure any trial programme so that each individual component is evaluated. Logically, a first step would be to evaluate the effect of cyclophosphamide followed by GCSF for stem cell mobilisation, while storing the stem cells for subsequent use in transplantation if evidence emerges that this would be justified.

#### HEAVY IMMUNOSUPPRESSION

The immunosuppression used in some mobilisation regimens (for example cyclophosphamide 4 g/m<sup>2</sup>) is in excess of that currently used for treatment of inflammatory bowel disease. Any initial steps into transplantation should probably be seen as immunosuppression with stem cell harvesting for rescue. If transplantation is performed, there is a strong argument for one trial arm to stop at the mobilisation and harvesting stage. If patients have a clinical response to the mobilisation regimen then the stem cells could be preserved for later high dose therapy and transplantation at the time of any subsequent relapse.

#### OUTCOME MEASURES

The existing data on stem cell transplantation in Crohn's disease have involved rather informal assessments (not unnaturally because it was not the reason for transplantation), with little formal histological evaluation.<sup>8 9 21-23</sup> Rigorous objective consensual measures would need to be established if any programme of transplantation in inflammatory bowel disease were to be undertaken.

#### SEQUENTIAL ANALYSIS

Equally important would be ongoing analysis by a safety board. Because of the potential for harm as well as good, a sensitive statistical approach, probably involving a sequential analysis,<sup>35</sup> would be needed. Data collection through the standardised data sets, to be agreed, would be appropriate.

#### MECHANISTIC ISSUES

Because neither the pathogenesis of inflammatory bowel disease nor the mode of action of autologous stem cell transplantation in autoimmune disease is known, a trial setting is particularly important to allow informative mechanistic studies to be conducted. Controversial though the persisting suggestions that inflammatory bowel disease may have an infectious aetiology are, they prompt concern that there could be circumstances where the process of intense immunosuppression and stem cell transplantation could be harmful.<sup>36</sup> Several studies suggest that the luminal



flora plays an important role in pathogenesis so that disease activity can be influenced by some antibiotic regimens.<sup>37,38</sup> Current antibiotics used in stem cell transplantation may well select pathogenic bowel organisms. Studying stem cell transplantation in inflammatory bowel disease in a trial setting would enable differing antibiotic regimens to be studied that may limit exposure of the naïve T cell clones that repopulate the mucosa to critical bacteria. It would be equally important to study mucosa immunology following stem cell transplantation because inflammatory bowel disease differs from other autoimmune conditions in that the mucosal as opposed to the systemic immune system is at least to some extent involved.

## Conclusions

Stem cell transplantation for inflammatory bowel disease may be inevitable. However, we hope that enthusiastic therapists will wait until the issues we have raised are resolved, that they will act within a cooperative trial setting, and that they will stop if such a trial approach suggests little or no benefit.

We thank Miss Laura Garratt for typing this manuscript.

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