Stem cell treatments of rheumatoid arthritis and the implications of their use in treating the condition

BY

Samuel House

Mark Strangwood

Grade awarded: Pass with Merit
Abstract

Stem cells are one of the most exciting and promising medical research areas being looked into in the present day. By providing an opportunity to develop an unlimited range of body cells from one base cell, they could be the secret to treatment of many debilitating and life-threatening conditions, and are already being used in preliminary trials and tests for some diseases. One such condition which affects between 0.5 – 1% of people in industrialized countries is rheumatoid arthritis. By causing a progressive degradation of the joints within the body, it can greatly reduce quality of life for those diagnosed and can affect anyone. Although numerous treatment programs exist to keep it in check, there remains no cure. In this project we will be exploring some of the possible applications of stem cells, and examining possible issues with their use.

Introduction

Adult stem cells are different from embryonic stem cells because they are not pluripotent: they are only able to differentiate into cells from the tissues they come from. Some types of Adult stem cells, hematopoietic blood forming cells, have in fact been used in transplants for 40 years, so their use is not new. The treatment using them has been improved however, as scientists are now extracting stem cells from the bone marrow in transplants and transferring the cells across as opposed to directly transplanting the bone marrow [7]. However, due to the limitations in the number that can be produced outside the body along with the cells into which they will differentiate, stem cells can only be used in certain circumstances. Embryonic stem cells are derived from stem cells that occur in embryos left over from in-vitro fertilization. Medically they are useful because of their ability to differentiate into every other type of cell in the body due to their pluripotent nature. [5] The process of using embryonic stem cells involves cultivation outside of the human body. The cells replicate in a petri dish where they are given a source of nutrition through feeder cells. They can be left in this state and can eventually end up producing millions of stem cells,
from just a few original cells. These cells can then be frozen and shipped to laboratories where they can be used in experimental treatments.

The cause of rheumatoid arthritis is not yet completely understood. The condition causes swelling in the joints, through an inflammatory response in the synovium (a protective membrane that secretes the fluid to keep the joints lubricated) and other joint tissue. The cause of swelling is believed to be the result of a build-up of cytokines (small proteins that play a key role in cell signaling), which are excreted by T lymphocyte cells in an autoimmune attack. The inflammation can be present in both singular or multiple joints and most commonly occurs in the smaller joints of the hands and feet. As time passes and the inflammation continues it can wear down both the bones and cartilage of joints, leading to a deformity in the joint. A demonstration of this can be seen on the following X-Ray.

The disease does not remain limited to the joints however, as it also affects the major organs of the body through development of Rheumatoid nodules. These nodules can occur on both the surface of the skin and also inside of internal organs. As a presumed, direct result of this, the risk of CVD (Coronary ventricle disease) is increased by 50% in those with Rheumatoid Arthritis, as demonstrated by Aviña-Zubieta JA (2008) [3]
50% of the risk of developing rheumatoid arthritis is down to genetic factors, as shown by Scott DL (2010) [1]. These factors are therefore outside of a patient’s control, and the disease subsequently cannot be avoided by managing lifestyle choices effectively. Smoking does account in part for whether or not someone will develop the disease however, as smokers are twice as likely as non-smokers to develop the disease [2].

At present, rheumatoid arthritis is treated primarily with auto-immune suppressants. Although these drugs often work relatively well, they also reduce the effectiveness of the immune response against foreign invaders [8]. One example of these drugs is Methotrexate, which also increases the risk of developing melanoma and lung cancers in patients [9].

Potential stem cell treatments for the condition may utilise Mesenchymal stem cells that are pluripotent, because they are able to differentiate into bone, cartilage and fat cells. This property would be key when used in the treatment of RA as it could regenerate the tissue damaged by the wear and tear on the bones. One of the other properties of these stem cells is their ability to generate area-specific auto immune suppressants, meaning that the body’s entire immune system wouldn’t have to be compromised to allow for the disease to be treated. The reason for these suppressants is that the Mesenchymal stem cells carry out the synthesis of interleukin-10, an anti-inflammatory cytokine which serves to create a micro environment of reduced inflammation.

The cells are also hypo-immunogenic, lacking the ability to perform MHC and co-stimulatory molecule stimulation. MHC’s normal purpose is to bind peptide fragments and display sections of the fragments for recognition by the necessary T cells. However when this process cannot occur, the immune system will not attack the MHC lacking cells. The lack of Co-stimulation also avoids the activation of T cells. In addition to this the Mesenchymal cells also prevent immune cell response through the disruption of CD4+ T cell functions. These cells are T-Helper cells that aid MHC presenting cells by the release of cell signaling cytokines, further avoiding triggering an immune system response [10]. Together these adaptations result in successful treatments of RA through the injection of them into infected areas, as they both reduce inflammation, regenerate tissue, and avoid triggering an immune system response to foreign cells.
Discussion

Ethical Implications

For the foreseeable future stem cells treatments will not be available on a large scale. As they’re a new treatment their effectiveness must be assessed and evaluated before their usage becomes widespread, and despite their currently limited applications, questions are already being raised over the ethics of their use.

One of the most loudly debated points over the use of stem cell treatments is whether or not using them constitutes the destruction of life. Supporters of this point of view might point out that the entire purpose of embryonic stem cells is to help create life; using them in a treatment therefore constitutes the destruction of life.

Opponents of this perspective may emphasize that as the stem cells are taken from spare embryos from IVF treatments, they never would have developed further than the embryonic stage. To try and gain a sample of people’s views we took a sample of as many people as we could using an online survey service.

We asked people to discuss whether or not they believed the usage of stem cells was appropriate in certain scenarios [21]. Overall, the survey respondents support the use of stem cells in the severest of cases. For example, for the first scenario “The person has severe problems with mobility, requiring help to get dressed and perform basic activities”, the vast majority of people believed that the usage of stem cells in this scenario would be justified. 80% agreed, and from this we can infer that the usage of stem cells in treatment of life-threatening diseases would be accepted by the majority of people, as they deem that the benefits would outweigh the risks.

People were less sure about the second scenario, however, in which “The person has moderate problems with mobility, occasionally requiring help to get dressed”. People were more divided about whether or not the use of stem cells was justified in this scenario with 47% agreeing and 25% disagreeing. This implies that when the disease is potentially considered less serious, people begin to become more cautious about the use of stem cells. This data therefore suggests that although people generally believe that the use of stem cells is acceptable in the most severe cases, not everyone believes that their use should become widespread and should be used to treat all cases of the disease.

This idea is reinforced by the third scenario described by saying “The person has limited problems with mobility, but still struggles to exercise to a healthy degree”. People were almost evenly divided about whether or not the use of stem cells was justified in this scenario with 35% agreeing, 26% disagreeing, and 39% being unsure on the issue. This agrees with the point about people being less keen on the use of stem cells the less serious they consider the disease.
The trend continues with the results for the 4th and 5th questions. In the 4th, respondents were given the statement “The person has limited symptoms but has an extremely negative outlook on their future”. The use of stem cells in this situation garnered the support of 33% of the respondents, with 31% of the respondents disagreeing. This demonstrates the point where the respondents believed that the severity of the symptoms and the ethical implications were of almost equal importance, as those disagreeing reached almost the same level as those agreeing with the use. Question 5, in which “the person has limited symptoms but a positive outlook on their future” subsequently shows a reversal of the trend in the data, as the number of people who agreed with the use made up only 19%, whilst 55% disagreed.

Overall the trend in the surveys shows that as the scenarios become less serious from questions 1 to 5, the proportion of people who were willing to support the use of stem cells decreases. This suggests a wariness in regard to their use, as people evidently view them as acceptable, but not for widespread and unregulated usage.

**Economic Cost**

Despite only affecting around 400,000 people in the United Kingdom [11], a relatively small number compared to other conditions, rheumatoid arthritis costs the NHS £560 million per year [18], and the estimated cost to the economy is predicted to be between £3.8 billion and £4.75 billion annually [12].

There are many reasons that this cost is so high. Firstly, rheumatoid arthritis can commonly lead to a myriad of other, more serious issues, such as an increased risk of heart attacks, strokes, and even cervical myelopathy, where the irregular movement of the joints at the top of the spine can put pressure on the spine, possibly causing damage to the spinal cord [13]. These often more dangerous conditions can have a further cost, and the cost of caring for one rheumatoid arthritis patient on the NHS can therefore be much higher than the costs for other conditions, as doctors are effectively required to treat more than one illness.

Further to this, because of the nature of rheumatoid arthritis, in that it directly damages the joints, physiotherapy is often required alongside the medicines which are used for the disease. The use of such therapy allows patients to retain a greater range of movement in their daily activities, and is therefore a necessity for ensuring patients can retain a good quality of life with the condition [14].

Another reason for the high cost is that symptoms of rheumatoid arthritis can differ substantially from one patient to another. Research completed by the Arthritis Research UK shows that 75% of sufferers experience ‘joint pain, swelling and flare-ups’, 20% experience only ‘very mild rheumatoid arthritis’, and 5% will ‘develop severe disease with extensive disability’ [11]. This 5% of patients with extremely limited mobility are part of the reason why arthritis costs are so high, as the patients who are affected in such a way will require a great amount of support just to complete their daily activities, needing helpers and careers. They will also be totally unable to work, and need benefits and support from
the government. It is this which accounts for the cost to the economy between £3.8 billion and £4.75 billion each year [12].

It is because of this great cost which already exists in rheumatoid arthritis care that stem cell treatments for arthritis sufferers may be a viable, and even perhaps a cost-effective, choice for the NHS and its budget. If the use of stem cells was employed to treat the condition, there may be the potential for a full cure for the disease, rather than needing a reliance on the preventative medicines currently used to treat sufferers. In many cases these preventative medicines can be very costly themselves.

One example of such a medicine is Tocilizumab, which works by inhibiting the activity of interleukin-6, a cytokine involved in the auto-immune response, and through doing so reduces the inflammation of joints [15]. This medicine is moderately effective, but can cost a patient weighing 70kg £9295 annually [15]. To compound this cost, because of the nature of the drug, in that it only suppresses the inflammation and doesn’t prevent the auto-immune response from occurring, a patient may have to take the drug annually for the rest of their life. Assuming the patient lives with the disease for around 20 years, the lifetime cost will be around £185,900 (using the annual cost sourced above), for a treatment which may not even remove all joint pain or reduced mobility. In addition, this cost does not include physiotherapy, wages lost from time off work, or specialist equipment needed.

Although this figure is obviously high, it is difficult to compare quantitatively with the potential cost of a stem cell treatment, as treatments are not widely available clinically, and those available with private companies have a cost dependent on the specific patient and treatment selected [16]. However, allogenic stem cell transplants for other conditions such as cancer cost around $100,000 (£65,000), and it can be presumed that because the process is relatively similar for most stem cell transplants, the cost will be comparable to this figure [17]. Even if the treatment was assumed to be twice this, it would still prove to be less costly than the lifetime cost of preventative medicine for a patient with rheumatoid arthritis.

Using stem cells could therefore prove an economically viable decision for the NHS and the United Kingdom as a whole, as, if successful, it could allow a cure for patients so they may go back to jobs and normal life, rather than having to rely on expensive drugs for however long they live with the disease.

**Effectiveness of Treatment**

On the other hand the effectiveness of the stem cell treatments themselves has yet to be properly demonstrated, even though certain treatments related to embryonic stem cells have been trialled. The trials that have been conducted have proven promising. A trial was conducted in which an anti-inflammatory cytokine was transferred across to a special immune system presenting cell, a dendritic cell. This dendritic cell then acted on the body’s T-helper cells to prevent the immune system attacking the cells in the body. In addition to this, the dendritic cells also helped to prevent the breakdown of the bone material and the
subsequent transfer of the calcium into the bloodstream. The results of the test are described as demonstrating “that systemic administration of DC/FasL is able to suppress collagen-reactive T cells, resulting in effective and sustained treatment of established CIA.” [19] This suggests that the treatment will be effective because it is able to suppress the immune system for a sustained period of time, and because it can treat established cases of the disease, so is not limited to treating freshly diagnosed patients.

Embryonic stem cells can be made to differentiate into the dendritic cells. This is useful as it has proven to be particularly difficult to isolate the cells on their own so it is vital to have an abundant source, as described by Thomas Hügle (2008). [20] The successes achieved with dendritic cells prove that there is already at least one method of stem cell therapy which can be effectively implemented as a treatment.

Embryonic stem cells can also be used to repair the joints themselves by rejuvenating the cartilage which reduces the grinding of the bones. They can be turned into stromal stem cells, which can then in turn differentiate into chondrocyte cells, which are what can repair the cartilage. This treatment might prove to be effective with embryonic stem cells because it is hard to get adult stromal stem cells to propagate in the laboratory. As the principle has already been proven it shows that the embryonic stem cells might be effective as they can provide a plentiful supply of chondrocyte cells.
Conclusion

In conclusion, the employment of stem cells to treat rheumatoid arthritis, a debilitating and even life-threatening condition, has the potential to drastically improve the quality of life of sufferers by a factor which cannot be provided by current therapies or medicines, and even provide a route to a lifelong cure, for which there is currently no option available. Analysis of the costs may also suggest that the economic cost of treatment would be offset by the savings made on the need for medication or physiotherapy for those suffering from arthritis.

This is not however, to say that there is not a myriad of potential issues. One could understandably argue that people may refuse to have stem cell treatment, because of the amount of debate over the ethics of the use of the cells, and therefore any cost savings may not occur on the scale suggested. The cost of research and development could therefore have been wasted.

However, if our survey results could be taken to represent the views of the overall population, we could make an assumption that in the most severe cases such as those outlined in question one of our survey, in which a patient has massive mobility issues as a result of arthritis, people would be willing to accept the use of stem cells as treatment. It is in these severe cases in which the patient would be having the largest cost on the NHS, as their needs would need to be met through physiotherapy, expensive medicines, and maybe even psychological support for those who are struggling to cope with the effect their disease has on their life. It could therefore be argued that stem cells would still be a cost effective treatment for this reason, and not an impossible goal for the NHS.

It should be noted, on the other hand, that our survey did not involve interviewing actual rheumatoid arthritis patients, but was instead carried out to understand public consensus on the treatment. The responses of actual patients may actually differ, so such research would need to be carried out before any effective judgments could be made. The survey also only tested the views of 56 people [21], which is a relatively small sample size, so may not be totally representative of the overall population's views. Additionally, as a result of using the internet and social media as a platform to both promote and display the survey, our sample was made up of mainly younger people within our own age group, who may hold different views to those of an older age group.

As a treatment for rheumatoid arthritis, and indeed countless other conditions, stem cells therefore remain a distinct possibility. At the current stage of understanding, however, it isn’t possible to successfully implement them in an effective, economically viable, and safe treatment plan without crucial further research into how they affect the body, and detailed understanding of the mechanisms involved in how they could cure arthritis.
References

    Number of people worldwide that suffer with Rheumatoid arthritis and the genetic risk factor
    Scott DL, Wolfe F, Huizanga TW
    (2010)

[2] http://ard.bmj.com/content/69/01/70.abstract

    Smoking increasing the risk of Rheumatoid Arthritis


    Increased risk of CVD –
    Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Eteman M, Esdaile JM, Lacaille D.
    (2008)

[4] Figure 1
http://commons.wikimedia.org/wiki/File:RheumatoideArthritisAP.jpg#mediaviewer/File:RheumatoideArthritisAP.jpg

    X-Ray of someone's hand suffering from rheumatoid arthritis
    Dr. Martin Steinhoff


    The definition of pluripotent stem cells


    Statistics on the number of stem cells that are produced outside of the human body.


    Sanford’s transplant process


    The stem cell treatments for RA


    Increased risk of cancer (Melanoma and Lung) by Laurie Barclay, MD

Mesenchymal cells and avoiding triggering an immune system response


The number of arthritis sufferers in the United Kingdom


Economic costs of rheumatoid arthritis to the NHS in the United Kingdom


Details of the potential complications of rheumatoid arthritis


Benefits of physiotherapy for rheumatoid arthritis


Information on the mechanism behind Tocilizumab, a rheumatoid arthritis drug


Example of a website of a company offering stem cell treatments for a range of conditions


Information on cost and process of a stem cell transplant for a similar condition


Effectiveness of provision in the NHS for people suffering from rheumatoid arthritis


The effectiveness of antigen presenting cells in mice

[20] [http://arthritis-research.com/content/10/5/217](http://arthritis-research.com/content/10/5/217)

Trials using dendritic presenting cells

Thomas Hügle and Jacob M van Laar
Graphical representation of our own survey data —

Samuel House and Mark Strangwood