Live cell therapy: historical aspects, mechanisms of action, safety and success stories

Abstract

Therapeutic applications of xenogeneic remedies and various forms of cell therapy can be traced back in history for many centuries. However its clinical application in conventional medicine started in the beginning of 20th century from Switzerland and Germany. Current paper highlights the milestones of development of live cell therapy as a paradigm of regenerative medicine, discusses mechanisms of its biological function, safety of cell therapy and offers a series of case reports.

Keywords: cell therapy, live cell therapy, regenerative medicine, biomolecular therapy

History of the future

When Susruta and Archilles first used animal substances to treat ailments, least did they know it was an advent of the impossibilities. The earliest documents of Papyrius of Eber and Materia medica of Aristotle and Pliny The Elder (AD 23–79) substantiates that animal organs or extracts of it were used in medical therapy. Sixteenth century saw Paracelsus preaching ‘similia similibus curantur’ which translates ‘likes are cured by the likes’. In accord, yesteryears give us an account of the use of animal organs or extract in treating organ related ailments. Hunter, Berthold, Claude Benard and Brown-Sequard were among the pioneers who have used organ extracts to treat ailments.1–3

Exposing the existing pathological cells to its younger ones (i.e. embryonic, fetal or neonatal cells) have shown to revitalize and restore its physiological function. This in turn heals the organism in whole, biologically. This has been coined as ‘Cell Therapy’ by Paul Niehans, a Swiss doctor who routinely used it in his daily busy practice, in 1931. The puzzle became more apparent when Haberlandt prove that drying cells produce hormones that stimulate the growth of new ones. In the contexts of cell therapy, every single human being is made up of trillions of individual living units, cells, capable of metabolism, excretion, regulation and replication. It is when these individual units suffer, in whole, makes the human ill. This is cellular pathology, devised by Virchow. He called cells the “life bearers.”1–4

It was a pertinent discovery by Mall and Rud. Abderbalden, that substitution of the depleting substance by an organ will not restore its normal physiological function and continuous supply of large amount of hormones may cause disturbances throughout the whole endocrine system. History would recall that back in 1771 and 1849 respectively, Hunter and Berthold proved the effect of replacing the testicles of a castrated cock while in 1857, Claude Bernard the French Physiologist described the secretions by these organs, or rather endocrine secretions.3 In 1912, Küttners, working with thyroid tissue, stepped ahead and suggested that instead of organ grafting, the repetitive injection of vital organs will result in longer lasting effect. Later Küttners’s work was continued by Kurtzahn and Hübener.3 Both have reported a transplantation of the thyroid tissue via injection in treatment of children with myxoedema in 1927. Subsequently, in 1929 Henschen was reported to carry out similar works.1,5

It is notable to mention, from 1927, Niehans, transplanted various organs itself to treat sick subjects. Among which was practiced were transplanting the anterior lobe of hypophysis of a calf to a dwarf, anterior lobe of hypophysis of a sheep to a woman with amenorrhea and posterior lobe of hypophysis with the hypothalamo–hypophyseal tract to a patient suffering from diabetes insipidus. All these yielded success and the patients positively responded to the grafting. Niehans performed an astonishing, more than a thousand of organ transplants.

In 1931, Paul Niehans saved Professor De Quervain’s moribund patient who suffered from refractory tetanus after accidental removal of parathyroid glands during thyroidectomy. A suspension of ox’s parathyroid gland in physiological saline did not only save the patient’s life but surprisingly didn’t provoke any immune response. And this kept the patient symptom free for twenty six years! Dr. Paul Niehans paved the future of Cell Therapy. Following this success, with great precaution, he tried injecting cells of various organs into the muscle by harvesting them from the young animals or the fetus. Niehans recorded success, even among the severely ill patients. Following this success, in 1937, Niehans went on to use tissue culture and injection of the cultures in treating sick human and animals. In 1945, Niehans and Dr. I. Writh continued working on these experiments on the Institute of Pathology, University of Geneva. The years 1948 and 1949 saw further progress. Niehans with Prof. K. Fr. Bauers tested the therapeutic effects of vital preserved cells in Switzerland. Niehans and Professor A. Pischinger went on to examine the anti-cancer properties of fresh cells and further managed to preserve fresh cells by deep freezing and drying it in vacuo, with the help of engineer L. Schwander, using the Altmann method.1,5

Replace or replenish?

It was unanimously proven that injecting the cells as whole and not just the fragments or extracts that yields the desired therapeutic effects. Neumann demonstrated a long lasting cyclical estrus and anestrus condition in mice compared to just injected oestradiol, the hormone, that didn’t give a lasting effect. Bernhard noticed similar effects by injecting fresh human placental cells and preserved cells from hypothalamus and ovary to women suffering from premature physiological changes. They started having regular menstrual cycles lasting from few months to one and a half year. Von Schubert went...
on to inject placental cells from animals carrying female fetus to menopausal subjects, demonstrated a reversal of atrophic vaginitis. Amazingly, the cells injected did not contain traces of prolactin or sex hormones. Lorenz recorded a similar discovery when he treated subjects suffering from X-rays by injecting them with bone marrow cells which could not be done with cellular fragments or extracts.9,3

Hormones have temporal and dose dependent effects in a human body. The simplest example would be insulin which is only produced and secreted in a certain amount, when needed. Pancreas doesn’t synthesize and store excessive insulin to be used later. Hence therapeutic effect is obtained by injecting the organ cells rather than the products. It is also learned that organs function temporally and cyclically and each organ produces numerous different hormones which function in the complex regulation pathway as whole. However, the temporal relationship of an endocrine organ may potentially pose difficulties in cell therapy, knowing that a single organ may produce multiple hormones to regulate the functions of it or even other organs.5,10

The defence-ferment reaction described by Professor Emile Abderhalden was a very useful tool to evaluate the degree of organ damage. Organs with pathological changes secrete certain proteinase fragments that will denature albumin isolated from the specific organ. In vitro, this enzyme will precipitate the albumin and quantitative analysis of the precipitate gives an idea of the degree of the organ damage.

In modern days, cell therapy has been proven to yield astounding success among patients who have suffered chronic illnesses. Cell therapy has been successfully used in chronic endocrine disorders such as diabetes mellitus and hypothyroidism, cardiovascular diseases, neurological conditions, chronic kidney disease and even blood dyscrasias such as thalassemia. There are two types of cell preparation existing at the moment for the purposes of regenerative medicine – live cultured precursor/progenitor cells that were discussed in some of our previous publications11,12 and cryogenically preserved live cells, also known as frozen organo cryogenics. The safety and clinical efficacy of the later are discussed in the paragraphs below.

Cell therapy: safety and efficacy

The safety and efficacy of cell therapy has been the main concern of researchers over decades, ever since cell therapy has been employed in managing an array of disorders. Longitudinal studies with detailed archive of patients and treatment information are well kept and studied years after years, proving that cell therapy are equally safe and effective. Cross sectional studies are also used from time to time to determine the safety profile and efficacy of a certain type of method or cells used. This is to ensure patient’s safety and assurance.

One such research concerned of the safety of cell therapy was carried out in Germany. The research was carried out in March 2018. 189 patients were chosen as respondents. Their medical records and demographic data were collected well in advance and a questionnaire comprising the risk and benefit and a separate sheet for the reporting of any adverse effect was despatched. Research participants were also inquired of how they felt upon completion of the treatment, if they’ll repeat the treatment and would recommend it to their family and friends. The questionnaire was vet thoroughly to avoid confusing and leading questions. Written consents were obtained from the participants.

Three respondents were rejected due to various errors and a total of 186 questionnaires were analysed in most meticulous manner by field experts to retain the authenticity of the data and to ensure an unstained outcome. The highest number of respondents came from Indonesia followed by Philippines, Germany and Thailand. However, 56 questionnaires failed to indicate the country of origin. Mean age of the respondents were 56, age ranging from 1 to 95, where 83 were men and 108 were women.

All patients presented with a number of chronic degenerative age-related disorders. General rejuvenation and supportive treatment for the existing chronic diseases were the main indications to commence cell therapy. Cell therapy was done with xenogenic organ-specific cryogenically preserved live cells. Provided treatment had a synergistic effect with the existing medications those patients were on that resulted in reduction either cessation of intake of some of the medications that patients were taking for treatment of their chronic conditions or in significant reduction of the dose. A total of 183(98.4%) participant reported of feeling better after completion of the therapy and 182(97.8%) were affirmative of repeating the therapy. 184(98.9%) patients who saw the success of cell therapy were sure of recommending it to family and friends.

The research concluded that cell therapy was well tolerated and is safe. However a longitudinal and on-going follow up is vital just as the post marketing surveillance of modern medicine. Confounding factors contributing to the symptoms experienced by the patients have to be delineated and rule out to have not caused the said symptoms. A larger number of respondents are desired to draw a generalised conclusion.

Case reports

In the case of Mr. MZ, a 54 years old gentleman from Middle East, cell therapy has been evidentially successful. On February 23rd, 2017, Mr. MZ presented to the European Wellness Centre with symptoms of dyspepsia, lethargy, low sex drive and chronic stress. He also suffered from gastro-esophageal reflux disease, fatty liver with underlying thyroid disorder and diabetes mellitus for 13 years. Diabetes Mellitus is a chronic endocrine disorder, left untreated, may lead to various complications and might even mortality. Further history revealed he had symptoms of hormonal imbalance and also poor sleep quality. Mr. MZ had his first cell therapy session on 20th May, 2017. Cell therapy renders an ideal metabolic and glycemic state and further, prevents the complications of Diabetes Mellitus while fixing the other health issues. It helps in regeneration of the damaged organs involved, in Mr. MZ, pancreas, the tissues of the gastro-intestinal tract, the gonads and the nervous system. The poor glucose control could have been the single cause of Mr. MZ’s symptoms. However, further investigation is needed to rule out other disease conditions. Prior to the cell therapy sessions in May 2017 and June 2018, Mr. MZ underwent series of medical interventions to achieve optimal outcome. Diagnosis of his medical condition was made with thorough history, clinical examination and blood investigations. It was noted that the glycosylated haemoglobin level, corresponding to the blood glucose level was deranged, as well as the cholesterol level. Abnormal serum cortisol and free testosterone reflected the hormonal imbalance. He also had low vitamin D levels and his alphafo protein, a tumour marker was raised. As practiced in European Wellness, Mr. MZ underwent detoxification followed by cell repair. Among the methods employed were colon hydrotherapy, ozone, peptide therapy with cell
organ specific cell extracts, intravenous vitamins, lasers and Alpha Lipolic Acid(ALA) infusion. Patient was also subjected to personalised supplements and underwent yearly blood monitoring. He was compliant to all his medication and his follow ups. During his regular visits, his endocrinologist was able to taper down his medication and stop some. His second cell therapy session was in June 2018. Mr. MZ responded very well to the therapy and this was evident when symptomatic improvements were reported. He has been energetic and gets good sleep and no longer feels stressed. The routine blood investigations six months later improved from the baseline. Notable to mention, the glycosylated haemoglobin level decreased from 8.6% to 8.2%, corresponding to the reduction of the blood glucose level from 162 mg/dl to 132mg/dl. Serum cortisol reduced tremendously from 29.2ug/dl to a normal value of 17.0ug/dl. His free active testosterone levels showed the most significant improvement from 289.04ng/ml to 778.56ng/ml. All these point to a better endocrine function in whole.

Mr. MZ is delighted with the remarkable changes in the quality of life and health, both physically and by investigations and is excited and looks forward to attend more sessions with European Wellness and achieve ideal health. Endocrine disorders aren’t just the case. Mrs. CC first sought help on September 8th, 2017. She presented with complaints of joint pain, mainly around waist and neck, lethargy and symptoms of dyspepsia and hormonal imbalances. She also complained of having eye sight issues, poor memory and alopecia. Mrs. CC is known to have dyslipidaemia, subclinical hypothyroidism, hypovitaminosis D and prediabetic state. Her pre–treatment work up revealed a raised inflammatory marker of HS C–reactive protein (8.37mg/dl) and a significantly low level of Vitamin D (17.4g/dl). Her renal function, sex hormones, thyroid stimulating hormone and serum cortisol levels were normal. Glycosylated haemoglobin level was raised to 5.7%.

Upon gathering complete history and thorough medical examination followed by blood investigations, she was prepared for multiple modalities of detoxification and cellular repair among which were colon hydrotherapy, ozone, peptide therapy, intravenous vitamins and blood lasers. She also had regular liver detoxification infusions. Mrs. CC’s blood parameters were monitored regularly and she was put on personalised supplements. She had her first session of cell therapy session in October 24th, 2017. Mrs. CC has been compliant to all her medication and her appointments.

Mrs. CC’s presentation of chronic joint pains with alopecia and lethargy may give rise to many differential diagnoses especially connective tissue disease or a spectrum of auto immune condition. Taken as separate symptoms and given the age, she could also be suffering from degenerative spine disease with no neurological deficit. The pre-existing morbidity might have also given rise to the other symptoms. Cell therapy aims to regenerate the particular surfaces, cartilage and synovial membranes, the pancreas, thyroid and nervous system in general.

Upon completion of her cell therapy session, Mrs. CC’s condition was re-evaluated. Mrs. CC gave a good report of improvement of her symptoms. She was more energetic and her multiple joint pains reduced significantly. Repeated blood investigations five months later supported the regeneration of damaged organs. There was a significant increase in Vitamin D levels which normalised from a deficient amount of 17.5ng/ml to 31.8ng/ml. Serum free T3 and T4 raised to near optimal levels from 2.90pg/ml to 3.07pg/ml and 1.00ng/ml to 1.90ng/ml respectively. Inflammatory marker, HS C–reactive protein normalised from 8.86µmol/L to 7.82µ/L, denoting resolved acute inflammation. Glycosylated haemoglobin reduced from 5.7% to 5.6% improving the prediabetic condition. Sex hormones, testosterone and dehydroxyepiandosterone (DHEAs) though were in normal range, further increased to near optimal levels. These clinical and biochemical improvement delighted Mrs. CC and she continued her follow up to achieve ideal health.

Dizziness and vertigo may suggest an array of diseases from as benign as paroxysmal positional vertigo to cerebellar pathology. By and large, these most commonly but not always point to nervous system pathology. Mr. H.C., a sixty four years old entrepreneur presented to the facility in September 2013 with complaints of dizziness, vertigo and sensorineural hearing loss since 13 years ago, for which he uses hearing aid. He also suffers from poor memory and symptoms of hormonal imbalances. Mr. H.C. has known comorbidities of hypothyroidism and vitamin deficiencies.

After obtaining complete history, a thorough clinical examination was done and baseline investigations were taken. Mr. H.C. was noted to have stage 2 chronic kidney disease with an estimated glomerular filtration rate of 60 ml/min. He had a suboptimal sugar control with glycosylated haemoglobin level of 6.1% while his Vitamin D and testosterone levels were subnormal. He was also noted to have raised levels of serum cortisol.

As the protocol suggests, treatment of Mr. H.C. was augmented with detoxification and repair before proceeding with cell therapy sessions. Mr. H.C. was subjected to the whole range of regenerative therapies. Intravenous supplement of blood laser, multivitamins, AlphaLipoic Acid(ALA) infusion and periodic supply of parenteral vitamins were given. A personalised supplement plan was constructed and patient was ensured of compliance. Mr. H.C. underwent cell therapy with live cryogenic cells on the October 10th, 2017 and was followed up closely thereafter.

Upon completion of treatment, Mr. H.C. noticed significant improvement in the symptoms he initially presented with. The dizziness and vertigo assuaged while the laboratory parameters substantiated the success of therapy. A year later, his renal function notably improved from estimated glomerular filtration rate of 60ml/ min to 93.9ml/min, improving to chronic kidney disease stage 1. The Vitamin D and serum free testosterone levels improved from 13.7ng/ ml and 1.9ng/dl to 33.3ng/ml and 14.25ng/dl respectively while glycosylated haemoglobin level dropped from 6.1% to 5.9%, denoting a better glycemic control. Also noted was the significant drop of serum cortisol from 29.2ug/ml to 10.6ug/ml. Evidently, target organs such as the pancreas, the kidneys and nervous system in general were rejuvenated through cell therapy. However, the improvement of sensorineural hearing loss would be a long term process and warrants a long term therapy and continues follow up.

Mr. H.C. was excited and thankful for improvement in his health and looks forward to achieve better height in his health. He is eager to continue his treatment and has been compliant to the appointments set. The thyroid gland is a butterfly shaped endocrine organ located at the anterior part of the neck just below the ‘Adam’s apple’. It is responsible for the production and secretion of thyroid hormone. Thyroid hormone is one of the vital hormones that controls the metabolism and regulation of every single cell in the human body. Hashimoto’s thyroiditis is a medical condition where the cells responsible for the production of thyroid hormones in the thyroid

gland are destroyed by the auto–immune mechanism, resulting in hypothyroidism often presenting with a range of symptoms. Weight gain, abnormal menstrual cycle, coarse and dry skin, lethargy, decreased libido and constipation are among the notable few.

On September 22nd, 2017, Mrs. S.S, a 64 years old South-east Asian lady presented for consultation hoping to find cure for her Hashimoto’s thyroiditis that she has been having for the many years. Possibly due to the hypothyroidism, she also presented with alopecia, mild fatty liver, dyslipidemia and hormonal imbalances. Her other complaints include chronic back pain, dizziness and vertigo with headache. Apart from Hashimoto’s disease, Mrs. S.S is known to suffer from hypertension, prediabetic state and vitamin deficiency.

As a routine practice, Mrs. S.S had to undergo the detoxification, where periodic proprietary chelation therapy was used to eliminate heavy metals from the body and also the PlaQuX therapy. Following which cellular repair was done with ozone therapy, Alpha lipoic acid infusion and peptides therapy. Mrs. S.S was also given parenteral supplement of multivitamins and personalised supplement plan was drawn for her, by which she was compliant with.

Mrs. S.S received her first cell therapy a month after her initial visit. Baseline investigations in September 2017 showed normal levels of the blood parameters of concern. However, no baseline investigations for glycosylated haemoglobin levels, free triiodothyronine and thyroxine levels were found. Liver enzymes, acute phase reactants, sex hormones and homocysteine levels were within normal range. Vitamin D and both the thyroid hormones were subnormal while glycosylated haemoglobin levels were raised. Repeated blood parameters three months later showed tremendous raise in vitamin D and the thyroid hormone levels. Serum Vitamin D normalised from 18.3ng/ml to 51.4ng/ml while free triiodothyronine and thyroxine levels increased from 2.08pg/ml to 2.15pg/ml and 0.93ng/dl to 1.10ng/dl respectively. Glycosylated haemoglobin level reduced from 5.7% to 5.6%. The androstenedione or dehydroxyepiandrosterone (DHEAs) level saw a leap from 123.7ug/dl to 130.2ug/dl. Though within the normal range, the acute phase reactant HS C–reactive protein reduced significantly from 7.07mg/L to as low as 0.48mg/L. Corresponding to improving blood parameters, Mrs. S.S also reported on improving symptoms of headache and dizziness. Modern medicine has deemed Hashimoto’s disease as incurable and needs lifelong thyroxine supplement. However, cell therapy proved this otherwise.

Ulcerative colitis and hypothyroidism are among the many organs related diseases which are attributed to autoimmunity. In a nutshell, when the body’s own cells or antigens are seen as foreign by the host immune system, these cells are destroyed by an inevitable ‘self–destruction’ immune response by the host immunity. This can be an acute or a chronic health issue. Rheumatoid arthritis, ulcerative colitis, Hashimoto’s thyroiditis and systemic lupus erythematosus are just a very few to mention from a long list. Patients suffering from autoimmune diseases have to be on long term immunosuppressive drugs and along the way, suffer from opportunistic infection and succumb to the disease itself or the arising complications. Mr. R.K., a 54 years old gentleman hails from South-east Asia visited European Wellness facility with the hope of getting a solution for his ailments. He also presented with complaints of hormonal imbalances and recurrent infection. He is known to be suffering from multiple chronic illnesses namely hypothyroidism, ulcerative colitis, type II diabetes mellitus and also non-alcoholic steatohepatitis.

A thorough and comprehensive history was taken after which a complete clinical examination was performed. Baseline investigation was taken in December 2015. He suffered from stage 2 chronic kidney disease with estimated glomerular filtration rate of 70ml/min. Liver damage was noted with a raised gamma glutayl transferase level of 67U/L. Glycosylated haemoglobin levels were higher than normal range, 6.8%.

Mr. Y.O. had his system detoxification and repair followed by his first cell therapy in February 2016 and a second session year later. Blood investigations repeated ten months after the first cell therapy showed significant improvement in the renal function where the estimated glomerular filtration rate increased from 70ml/min to 94ml/min, shifting the staging of the chronic kidney disease from stage 2 to stage 1 with a drop in serum creatinine level from 1.13mg/dl to 0.89mg/dl. Liver function improved signifying the liver parenchymal rejuvenation. The gamma glutaryltransferase level normalised from 67U/L to 50U/L while blood glucose level reduced from 96 mg/dl to 92mg/dl. This is reflected by the reduction of glycosylated haemoglobin level reduced from 6.8% to 6.6%, though didn’t normalise. Serum Vitamin D level leaped from 18.2ng/ml to 28.4ng/ml. Other normal parameters which further dropped to optimal level include low density lipoprotein (LDL), from 84mg/dl to 58mg/dl, total cholesterol level from 172mg/dl to 105mg/dl and triglyceride level from 120mg/dl to 48mg/dl.

Upon completing his first cell therapy, Mr.R.K., opted to continue his treatment. Second session of cell therapy was done in February 2017. He is currently being followed up by his family physician and completed his third session of the cell therapy in 2018.

Gout or gouty arthritis is a type of inflammatory joint disease that can only be controlled through diet and medications. Modern medicine is still looking to find a cure rather than continuous or lifelong treatment. Purine is derived from deoxyribonucleic acid (DNA) metabolism, essential component of all cells. Uric acid is a by-product of purine metabolism, which accumulates in various parts of human body, particularly joints, leading to inflammation and excruciating pain. This is a life-long disease and demands adequate pain management and medications to regulate uric acid synthesis. To date, no medication has been found to fix, once and for all, the cause of persistent rise in serum uric acid. Gouty arthritis can be a debilitating condition, especially at later stage, with the formation of gouty tophi, deforming joints.

Mr. J.M. is a 26 years old Asian gentleman. He has been suffering from hypothyroidism and hypocalcemia for years and has been using metered dose inhalers (pumps) for his bronchial asthma. He also admits of recurrent clinic visits for psoriasis for years and reported of being told to have diffused fatty liver. Mr. J.M. came to The European Wellness Centre hoping to get a permanent cure for the problems he has battled the most, gouty arthritis and seizure disorder which has been demanding his time and energy for recurrent hospital visits. Mr. J.M.’s first visit to The European Wellness Centre was in January 2013 seeking medical advice and assessment. As per routine, initial blood and urine work up, detoxification and repair was done before carrying out the cell therapy. Mr. J.M. was subjected to chelation therapy to get rid of the heavy metals found in his serum followed by multiple vitamin injections and multivitamin infusions.

It is notable to mention that the baseline blood investigations of Mr. J.M. showed a raised chronic inflammatory marker, the erythrocyte
sedimentation rate (ESR) at a level of 24 mm/hour while the serum ionised calcium levels were multiple fold higher than normal range, 29.2µg/dl (1.12–1.32µg/dl). High levels of serum ionised calcium would indicate previously undiagnosed hyperparathyroidism. Thyroid function, lipid and renal profile and glycemic control generally appeared normal. His first cell therapy session was carried out on May 7th, 2013 and the second one on August 12th, 2014. He was put on personalised supplements to which he was compliant.

Repeated blood investigation showed much improvement from the baseline investigation, with improvement in even blood parameters which were within normal range. Glaring drop in the erythrocyte sedimentation rate from 24 mm/hour to 20mm/hour, approaching normal range signifying resolving inflammation while the serum ionised calcium fell from 29.2µg/dl to 10.6µg/dl substantiating improved function of parathyroid gland. Other notable parameters to be mentioned would be the drop in glycosylated haemoglobin level from 4.90% to 4.50%, a drop of total cholesterol from 155.21mg/ml to 134.69mg/ml and further drop in triglyceride level from 124.55mg/dl to 86.33mg/dl. Mr. J.M.’s affirmative response to the therapy was further substantiated with clinical improvement of his symptoms. His dry scaly and peeling skin improved much and he reported of very minimal similar complains with overall rise in energy level and confidence! He is currently being monitored by his family physician and is keen for further treatment.

Conclusion

The medical science has seen tremendous progress through past centuries with novel discoveries and astounding achievements. However, it is still perplexing that century old diseases are still deemed incurable. Cell therapy has proven to reverse such medical conditions with a good safety profile. The usage of this treatment method has to be widened and made as one of the main stream treatment modalities in near future. The efficacy, testimonies and safety profile should be kept under the purview of continuous surveillance to establish a reputable tract record as a support of evidence based medicine.

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Conflicts of interest

Authors declare that there is no conflict of interest.

References