BJMP

Volume 6 Number 4
December 2013

British Journal of Medical Practitioners

www.bjmp.org
ISSN: 1757-8515

British Journal of Medical Practitioners

Volume 6 Number 4 (December 2013)

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British Journal of Medical Practitioners

Volume 6 Number 4 (December 2013)

BJMP December 2013 Volume 6 Number 4

BJMP 2013;6(4):a633

Editorial

Intensive care resource allocation: when difficult choices have to be made

Marco Luchetti

Resource allocation in medicine applies to two complementary levels of care. One pertains to the organisation of public health and the provision of general rules informing the management of the system (macro-allocation). On the other hand, there is the need to specify decision criteria for the daily practice of health care providers who have to decide on the utilisation of their allocated resources, while dealing with a demand that often exceeds supply (micro-allocation).[1]

Beneficence, i.e. acting for the good of the patient, is one of the founding value of traditional ethics in medicine. However, the picture has changed when the core value of medicine shifted toward the centrality of the human person and the ideal of self-determination. The patient is now a 'health care user' who consults a professional whose knowledge and expertise is used in order to arrive at options. Good medical practice seems the result of a 'contract bargaining', which must take into account different criteria: clinical indication, patient preferences and subjective values, and appropriateness within the social context. Controlling how these three elements interact with each other requires a constant commitment and synchronised interventions.[2]

For cultural reasons, physicians consider, quite rightly, the costs of their interventions to be incommensurable with the life and the restoration to health of the diseased person. The most difficult problem in the distribution of resources remains the finding of convincing criteria to provide guidance, when often painful choices have to be made in the face of inadequacies in the availability of resources.[3]

Intensive care is one of the most expensive specialities of medicine and intensive care beds nowadays represent a limited resource.[4, 5] The lack of beds is a daily problem in many ICU[6, 7] and bed allocation has been considered one of the thorniest and stressful aspects of the intensivist's job.[8] Studies have shown that resource use is often inefficient in European ICU. One of the main reasons for this inefficiency has been identified as nursing force "waste".[9]

Monitoring and support of deficient vital functions are the main aims of intensive care. Usually, intensivists carry out the adequate diagnostic procedures and necessary medical and surgical treatments required to improve patient outcomes. There has been a considerable international effort to define the ethical, clinical and economical criteria for admission to ICU and to draft the relevant guidelines. The fundamental point is that resources should be utilised appropriately, i.e. that the patient be of the right category, in the right place and at the right time. Furthermore, ethics dictates that resources be allocated where they are more likely to make an impact.[10-13]

ICU admission and discharge can be ruled by means of a priority scale which classifies patients based on the expected benefit to result from intensive treatment.[14] However, while it may be relatively easy to create "on-paper" scenarios affirming that patients who are too critical or not critical enough to benefit should not be admitted to intensive care, identifying these patients in everyday practice is far from simple.

As far as a reasonable doubt may be considered regarding the irreversibility of the clinical status, it is appropriate to initiate or continue intensive treatment. On the contrary, if the irreversibility of the clinical setting is deemed to be reasonably certain, it is appropriate not to initiate or to withdraw intensive measures to spare the patient the undue prolongation of the dying process. Excessive treatment is ethically unfair and should be strongly condemned, because it determines an inappropriate use of the means of treatment; it is likely to cause harm and pain to the patient and fails to respect the patient's dignity in death. Excessive treatment also increases the suffering of family members, is frustrating for care providers and generates an inequitable distribution of resources by curtailing them for other patients. The withdrawal of an intensive treatment, which was previously initiated because deemed to be indicated and accepted, or because the patient's clinical status and relevant prognosis were not clear enough at the time, should be considered whenever the clinical picture counter-indicates treatment continuation, the patient withdraws consent, or a previously defined therapeutic limit is reached.[15]

Immortality has always been an ambition for human beings. Today's medicine appears to be instrumental in dealing with this type of issues by making promises that will be hard not to break. The most urgent form of action to be undertaken regards these unwarranted expectations that society holds about the

efficacy of medicine. The message to put across ought to be that death is inescapable and that the most severe diseases are incurable.

Once the inevitability of resorting to often dramatic measures in today's health care system is postulated, we are confronted with the problem of finding an ethical justification to subsequent decisions. On the basis of the choices made necessary by the paucity of available resources, medical treatment would be "apportioned", i.e., distributed according to commitments and rules, with the inevitable exclusion of some from the utilization of the services themselves.

Rationalisation, intended as best utilisation and fair limitation, is an economic necessity, juridically and ethically legitimate. The ultimate objective must remain that of equitable apportionment.

Competing Interests
None declared
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REFERENCES

1. Persad G, Wertheimer A, Emanuel EJ (2009). Principles for allocation of scarce medical interventions. Lancet 373: 423–31.
2. Daniels N (2001). Justice, health, and healthcare. Am J Bioeth 1: 2–16.
3. Berlinguer G (2004). Bioethics, health, and inequality. Lancet 364: 1086-91.
4. Szalados JE (2004). Access to critical care: medical rationing of a public right or privilege? Crit Care Med 32: 1623–4.
5. Cook D, Giacomini M (1999). The sound of silence: rationing resources for critically ill patients. Crit Care 3: R1–3.
6. Vincent JL (1990). European attitudes towards ethical problems in intensive care medicine: results of an ethical questionnaire. Intensive Care Med 16: 256–64.
7. Metcalfe MA, Sloggett A, McPherson K (1997). Mortality among appropriately referred patients refused admission to intensive-care units. Lancet 350: 7–11.
8. Coomber S, Todd C, Park G, et al (2002). Stress in UK intensive care unit doctors. Br J Anaesth 89: 873–81.
9. Iapichino G, Radrizzani D, Rossi C, et al (GiViTI Group) (2007). Proposal of a flexible structural-organizing model for the Intensive Care Units. Minerva Anestesiol 73: 501-6.
10. Sprung CL, Geber D, Eidelman LA, et al (1999). Evaluation of triage decisions for intensive care admission. Crit Care Med 27: 1073–9.
11. Society of Critical Care Medicine Ethics Committee (1994). Consensus statement on the triage of critically ill patients. JAMA 271: 1200–3.
12. American Thoracic Society (1997). Fair allocation of intensive care unit resources. Am J Respir Crit Care Med 156: 1282–301.
13. Task Force of the American College of Critical Care Medicine (1999). Guidelines for ICU admission, discharge, and triage. Crit Care Med 27: 633–8.
14. Gruppo di Studio ad Hoc della Commissione di Bioetica della SIAARTI (2003). SIAARTI guidelines for admission to and discharge from Intensive Care Units and for limitation of treatment in intensive care. Minerva Anestesiol 69: 101-18.
15. SIAARTI - Italian Society of Anaesthesia Analgesia Resuscitation and Intensive Care Bioethical Board (2006). End-of-life care and the intensivist: SIAARTI recommendations on the management of the dying patient. Minerva Anestesiol 72: 927-63.

BJMP 2013;6(4):a636

Research Article

A Study on Public Intention to Donate Organ: Perceived Barriers and Facilitators

Josephine R Little Flower and Balamurugan E

Abstract

Aim: Organ donation rate in India is very poor. The factors contributing to donating and not donating an organ is not well known. Hence, the present study was conducted to identify the perceived barrier and facilitator of organ donation among general public of Puducherry, India.

Method: A cross sectional explorative study was undertaken with a sample of 400 eligible subjects from the general public of puducherry. Each participant underwent a face to face interview with the help of a structured questionnaire; data collected was analyzed using appropriate descriptive and inferential statics in SPSS.

Result: Of the 400 subjects interviewed, the most common perceived barriers identified were opposition from family (82.8%) and fear (72.4%). The most common perceived facilitators were thought that organ donation would save someone's life (95.9%) and sense of improved humanity (95%). While associating the public intention to donate organ with select variables only educational status was found to be positively associated (p =0.001).

Conclusion: From the available scientific evidence it is conducted that the knowledge of organ donation remain still poor and the identified barriers and facilitators should be taken in the account while motivating the general public to donate organ in future.

Keywords: Organ Donation, Barriers, Facilitators, Intention.

Introduction

Organ transplantation is an effective therapy for end-stage organ failure and is widely practiced around the world. According to World Health Organization (WHO), kidney transplants are carried out in 91 countries. Around 66,000 kidney donations, 21,000 liver donations and 6000 heart transplants were performed globally in 2005. [1] In India the rate of organ donation is only 0.16 per million populations, compared to America's 26 and Spain's 35.[2] The shortage of organ is virtually a universal problem. Though many efforts were undertaken by the government to motivate the public towards donation of organs, the rate of organ donors has not paralleled the growing waiting list[3],[4], [5] and inadequate organ donation in India remains a major limiting factor for transplantation. There are several factors which could facilitate and hinder the general public to donate a organ. Identifying these factors could help in planning effective strategies to combat the problem. Hence the present study was conducted with the aim to explore the general publics perceived barriers and facilitating factors of organ donation.

Materials and methods

The present study was a cross sectional, exploratory survey conducted among the general public of Puducherry U.T, India. 400 eligible subjects who fulfilled the following criteria were included a) Subjects aged 18 and above, and b) who understand either the local language Tamil or English. Subjects with intellectual, psychiatric and emotional disturbances that could affect the reliability of their responses were excluded from the study. The population registry in the primary health centers of the selected community area was used as a sample frame to select subjects randomly. Every eligible subject was explained about the purpose of the study and signed a written consent form. Formal ethical clearance was obtained from the institute ethics committee before actual data collection procedure.

Preparation of the questionnaire

An extensive literature review was carried out to understand the possible barriers and facilitators reported in the past. Reported barrier and facilitating factors in the literature were included in constructing the questionnaire, including specific cultural and religious oriented items specific to Indians. Subject's intention to donate the organ was assessed using a single dichotomous question (yes or no). For assessing the barriers and facilitators related to organ donation a questionnaire with a total of 18 items (9 items each) was prepared in the form of closed ended question i.e. yes or no. Along with closed ended questions, an open ended question i.e. any other? was also included for obtaining an extended response apart from the framed questions. As knowledge is an important factor which could serve both as a barrier and facilitator for organ donation, 8 items related to knowledge were also included as a part of the questionnaire. Knowledge items of the questionnaire were evaluated by assigning a score of 1 for each correct response with a maximum possible score of 8. Interpretation of the knowledge component was also done by categorizing the knowledge as follows - Below 50% of the total score - Inadequate knowledge, 51 – 75% - Moderately adequate knowledge, above 75% - Adequate knowledge, for ease of understanding. The draft tool was validated for its content by 10 experts from the field of surgery, medicine, nursing, anthropology and psychology for its appropriateness. After

appropriate modification the content validity index for the tool was calculated and it was found to be highly valid (0.98). The reliability of the tool was estimated by a test re-test reliability method among 10 subjects with an interval of 2 weeks from the first and second time of administration of the questionnaire. It was found to be highly reliable with reliability coefficient of 0.91. A face to face interview method was used to collect data from each subject. Collected data was analyzed using SPSS for windows version 14 (SPSS Inc., Chicago, Il, USA) with appropriate descriptive and inferential statistics. A probability value of < 0.05 was set as the level of significance

Results

Basic Demographic details

Of the total 400 subjects enrolled the majority were male (56%), between the age group of 31-40 years (48%), and followed Hinduism (68%) at the time of interview. Most of the subjects were literate (70%) with education up to high school and resided in a rural area (53%).

Figure 1: Distribution of source of information regarding organ donation among the subjects.

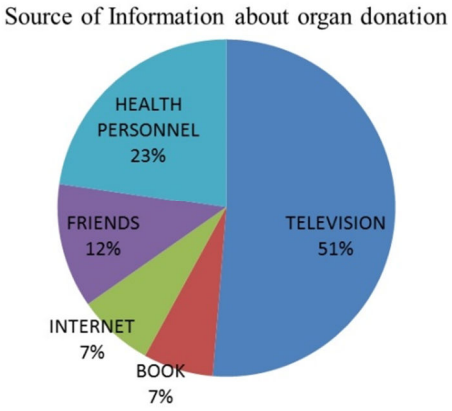

Table 1: Item wise distribution of different aspects of knowledge regarding organ donation (n=400)

S. No	Aspects of Knowledge	Correct response	Incorrect response
1.	Definition of organ donation	24%	76%
2.	Knowledge regarding Commonly donated organ	71.3%	28.7%
3.	Knowledge regarding Consent procedure for living donor	76%	24%
4.	Knowledge regarding Consent procedure after death	84.7%	15.3%
5.	Knowledge regarding Consent for mentally retarded person	41.3%	58.7%
6.	Knowledge regarding Consent for unclaimed dead bodies	35.3%	64.7%
7.	Knowledge regarding Organ matching procedure	85.3%	14.7%
8.	Knowledge regarding legal consideration for organ donation	56%	44%

Table 2: Perceived Barriers towards organ donation (n=121)

S. No	Barrier factors	Percentage
1.	Oppose from the family	82.8%
2.	Fear	72.4%
3.	Procedures are complicated	69%
4.	Affects physical appearance	65.5%
5.	Affects the future	58.6%
6.	Create psychological problem	58.6%
7.	Organs could be misused	55.2%
8.	Against religious belief	48.3%
9.	Insults human rights and dignity	48.3%

Table 3: Perceived Facilitators towards organ donation (n=279)

S. No	Facilitating factors	Percentage
1.	Save someone's life	95.9%
2.	Improve the sense of humanity	95%
3.	Save the life of a close relative	92.6%
4.	Wishes organ to be alive after death	92.6%
5.	To become a role model	77.7%
6.	Empathy for others	53.7%
7.	Rewarding experience	51.2%
8.	Due to family pressure	29.8%
9.	For economic benefit	27.3%

Knowledge regarding organ donation

The mean knowledge score of the subjects regarding organ donation was 4.74 1.45 score which ranged from a minimum score of 1 to a maximum score of 8. Most subjects responded correctly to questions related to organ matching (85.3%) and consent procedure (84.7%). Details of different aspects of knowledge regarding organ donation of the subjects can be found in Table 1. When subjects were asked about the source of information regarding organ donation, 51.3% of the subjects reported that they gained knowledge through television, 23% from health personnel, and 12% from friends and 7% through books and internet (Figure1). While categorizing knowledge scores the majority of the subjects (38.6%) had inadequate knowledge, 50.6% had moderate knowledge and only 10.6% had adequate knowledge regarding organ donation.

Intention to donate organs: Barriers and Facilitators

Of the total 400 subjects interviewed 69.75% of the subjects reported that they wish to donate their organs, whereas the remaining 30.25% reported that they will not donate their organs either during their life or after their death. Subsequently the factors for barriers and facilitators were also analyzed using the pretested questionnaire. The most common barriers perceived by the subjects related to organ donation were as follows, 'family opposition' (82.8%), 'complicated organ donation procedure' (69%), 'fear that donation affects their future' (58.36%), and 'misuse of organs' (55.2%). More

information about barriers is detailed in Table 2.The most important facilitating factors of organ donation as reported by the subjects were 'thought of saving someone's life' (95.9%), 'feeling of improved sense of humanity' (95%), 'to save the life of a close relative', 'thought that their organ live after their death (92.6%) and 'being a role model for others' (77.7%). More details of facilitating factor can be seen in Table 3

While associating the subject's intention to donate organs with demographic variables like age, gender, residence, education, religion, marital status, type of family and knowledge; only educational level had a significant association with the subject's intention to donate organ. Specifically graduate people are more likely to report intention to donate organ their organs than others (p<0.001).

Discussion

The current study was conducted with the aim to explore the general publics intention towards organ donation and to identify the perceived barriers and facilitators. The present study revealed that 69.7% of the subjects have an intention to donate their organs either during their life or after their death, which is similar to the finding of Chung et al[6] and Shahbazian H et al[7]. Similar to the previous studies[8] the current study also confirmed a positive association between public intentions to donate their organ with their educational status. Though many studies in the past reported attitudes[9],[10] of public towards organ donation, the present study was the first of its kind to analyze specifically the barriers and facilitators of organ donation among the general public, this adds strength to this study. The most common barrier reported in the present study was 'opposition form family in donating their organs'; these findings were similar to a previous study.[6] Illegal organ donation and misuse of organ is a major problem in India for the low organ donation rate among public[11], this fact was reflected even in the current study as 55.2% of the subjects reported misuse of an organ as barrier to organ donation. The most important facilitating factors of organ donation reported in the present study was 'thought of saving someone's life' (95.9%), 'feeling of improved sense of humanity' (95%), 'to save the life of a close relative' (92.9%), these finding were similar to the findings of Neelam et al conducted in India[12]. The majority of the respondents in this study reported "lack of information" about organ donation and transplantation. These findings are comparable with those reported from previous studies, which all indicate the importance of public education about the importance of organ donation[13],[14],[15],[16]. Our study identified that the principle respondents' source of information about organ donation was the television (TV). The contribution of other sources of information in providing respondents with knowledge about organ donation was minimal. Generally, studies had shown the importance of visual media in increasing the awareness of the public about organ donation. [17],[18]

Conclusion

Better knowledge may ultimately translate into the act of donation. Effective measures should be taken to educate people with relevant information with the involvement of media, doctors and religious scholars.

Acknowledgements
The author is grateful to all study participants who willingly participated in the study.
Competing Interests
None declared
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REFERENCES

1. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available information. Bulletin of the World Health Organization, 2007; 85: 901-980.
2. Srinivasan. India's rate of organ donation compares poorly with other countries'. Times of India. 3 August 2013: 3.
3. Shaheen F. Organ transplantation in the Kingdom of Saudi Arabia: new strategies. Saudi J Kidney Dis Transpl, 1994; 5:3-5.
4. Al-Shehri S, Shaeen F, Al-Khader A. Organ donations from deceased persons in the Saudi Arabian population. Exp Clin Transplant, 2005; 3:301-5
5. Aldawood A, Al Qahtani S, Dabbagh O, AlSayyari A. Organ donation after brain death: experience over five-years in a tertiary hospital. Saudi J Kidney Dis Transpl 2007;18:60-4
6. Christina KY Chung, CarolWK Ng, JackyYC Li. Attitudes, knowledge, and actions with regard to organ donation. Hong Kong Med J 2008; 14: 278-279.
7. Shahbazian H.Public attitudes toward cadaveric organ donation: a survey in Ahwaz. Urol J. 2006 Fall; 3(4):234-9.
8. Nahida Khan, Knowledge And Attitude Of People Towards Organ Donation. JUMDC , 2011; 2:15-21.
9. Diane L. Manninen, Public Attitudes and Behavior Regarding Organ Donation. JAMA. 1985;253(21):3111-3115. doi:10.1001/jama.1985.03350450083026.
10. H. El-Shoubak, Public Knowledge and Attitudes Toward Organ Donation and Transplantation: A Cross-Cultural Study.Transplantation Proceedings. 2005; 37: 1993–1997
11. Sunil Shroff. Legal and ethical aspects of organ donation and transplantation.Indian J Urol. 2009 Jul-Sep; 25(3): 348–355.
12. Neelam, A study of public attitude to donate their kidneys. Indian Journal of Advanced Nursing. 2013 ;1: 25-29
13. El-Shoubaki H, Bener A, Al-Mosalamani Y. Factors influencing organ donation and transplantation in the state of Qatar. Transplant Med 2006; 18:97-103.
14. Bilgel H, Sadikoglu G, Goktas O, Bilgel N. A survey of the public attitudes towards organ donation in a Turkish community and of the changes that have taken place in the last 12 years. Transpl Int 2004;17:126-30
15. Schauenburg H, Hildebrandt A. Public knowledge and attitudes on organ donation do not differ in Germany and Spain. Transplant Proc 2006; 38:1218-20.

16. Schauenburg H, Hildebrandt A. Public knowledge and attitudes on organ donation do not differ in Germany and Spain. Transplant Proc 2006;38:1218-20.
17. Matesanz R, Miranda B. Organ donation the role of the media and of public opinion. Nephrol Dial Transplant 1996; 11:2127-8.
18. Garcia V, Goldani J, Neumann J. Mass media and organ donation. Transplant Proc 1997; 29: 1618-21.

Research Article

BJMP 2013;6(4):a635

Impact of diabetes education and peer support group on the metabolic parameters of patients with Diabetes Mellitus (Type 1 and Type 2)

Issac Sachmechi, Aileen Wang, Paul Kim, David Reich, Hildegarde Payne and Vincent Bryan Salvador

Abstract

Aim This study was undertaken to investigate the effect of diabetes education (DE) alone versus diabetes education plus peer support group (DE+PS) in improving metabolic parameters in patients with diabetes mellitus (DM).

Methods We retrospectively included a total of 188 subjects with DM who were seen at the Diabetes Centre and Primary Care clinics at Queens Hospital Centre, Jamaica, New York. The patients were categorized into three main groups: (1) control group (n=62), who received primary care only, (2) DE group (n=63), who received primary care plus diabetes teaching from a certified diabetes nurse educator and (3) DE+PS group (n=63) who received education in diabetes and who joined a peer support group for at least two or more sessions. The mean change from baseline in hemoglobin A1C (HbA1C), weight, body mass index (BMI), systolic blood pressure (SBP), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG-C) was calculated after 3 follow up visits.

Results The patients in DE group were observed to have statistically significant decrease in mean HbA1C (mean change: -0.78%, p=0.013), TC (mean change: -16.89 mg/dL, p=0.01) and LDL-C (mean change: -11.75 mg/dL, p=0.04) from baseline to final follow. The same group also exhibited consistently significant reductions in HbA1C and LDL-C throughout from the third month to the thirteenth month of follow up. The patients in DE+PS group had a moderate decrease in HbA1C, SBP, TG-C and weight, and an increase in HDL-C, LDL-C and BMI in the final follow up, but all were not statistically significant.

Conclusion The present study suggested that participation in DE may assist with optimizing metabolic parameters such as HbA1C, TC and LDL-C levels in patients with diabetes. This benefit may perpetuate through time. The addition of peer support group to DE may or may not confer additional benefit.

Keywords: diabetes mellitus, metabolic parameters, diabetes education, diabetes peer support group

Abbreviations: DM – diabetes mellitus, HB A1C - Hemoglobin A1C (HB A1C), BMI - body mass index (kg/m2), SBP - systolic blood pressure, TC - total cholesterol, HDL-C - HDL cholesterol, LDL-C - LDL cholesterol, TG - triglycerides, ADA – American Diabetes Association

Introduction

Population-based studies indicated that diabetes remains as a nationwide epidemic that continues to grow tremendously affecting 25.8 million people or 8.3% of the US population.[1] This number is expected to reach 68 million or 25% of the population by 2030[2] as incidence of obesity is rising.[3]

The American Diabetes Association (ADA) recognizes diabetes education (DE) as an essential part of comprehensive care for patients with diabetes mellitus and recommends assessing self-management skills and knowledge at least annually in addition to participation in DE.[4] With the objective of improving the quality of life and reducing the disease burden, the ADA and the U.S. Department of Health and Human Services through its Healthy People 2020 program have emphasized three key components for effective disease management planning: regular medical care, self-management education and ongoing diabetes support.[5,6]

The hallmark of preventing the chronic complications of diabetes lies in optimizing metabolic parameters such as glycaemic control, blood pressure, weight and lipid profile. Pharmacologic intervention can only do so much in achieving treatment goals. It should be complemented with appropriate DE emphasizing dietary control, physical activity and strict medication adherence.[7,8] Adequate glycaemic control is clinically important because a percentile reduction in mean HbA1C is associated with a 21% reduction in diabetes-related death risk, 14% reduction in heart attacks and 37% reduction in microvascular complications.[9]

Diabetes self-management (DSM) education programs are valuable strategy for improving health behaviours which have significant impact on metabolic parameters.[10] This is supported by chronic care model that is based on the notion that improving the health of patients with chronic diseases depends on a number of factors that include patients' knowledge about their disease, daily practice of self-management techniques and healthy behaviors.[11,12,13]

A systematic review by Norris et al. has shown that DSM training confers positive effect on patients' knowledge about diabetes, blood glucose monitoring, and importance of dietary practices and glycaemic control.[14] In another retrospective observational study, evidence has suggested that participation in a multifactorial diabetes health education significantly improved glycaemic and lipid levels in the short term.[10]

Diabetes education/support group provides a comprehensive patient education, fosters a sense of community, and engages

the patients to become active part of a team managing their diabetes. The diabetes support group at Queens Hospital Centre provides services to a diverse population from different socioeconomic backgrounds and is offered to any patients with diabetes. It is facilitated by certified diabetes nurse educators in the hospital and in the clinic. Patients meet once a month per session and are provided education in self-management of diabetes, education in medication, diet, lifestyle modifications, regular exercise, weight management and translation in their respective languages, if needed.

Few researches have been conducted comparing the efficacy of DE and combination of diabetes education and peer support group (DE+PS) in improving the metabolic parameters of patients with DM. In patients with DM, the primary objective of this study was to assess the clinical impact of DE and combined DE+PS group on metabolic parameters such as lowering HbA1C, reducing weight or BMI, controlling blood pressure, and improving lipid profile.

Methods

The study subjects were identified through retrospective review of electronic medical records of adult patients aged more than 18 years old with diabetes and being treated at the Diabetes Centre and/or Primary Care Clinic of Queens Hospital Centre, Jamaica, New York from January 01, 2007 to June 01, 2011. A total of 188 study subjects were selected and assigned to three groups: (1) control group (n=62), who received primary care only, (2) DE group (n=63), who received diabetes teaching from DM nurse educator in addition to primary care, and (3) DE+PS group (n=63), who received both diabetes education and attended at least 2 or more sessions of peer support group in addition to primary care. The subjects in control group, education group, education plus peer support group were matched on age, sex, weight and BMI. Considering the data availability, the duration of follow up measured in each group varied; the control group was followed up for 8 months, the DE group for 13 months and the DE+PS group for 19 months. The changes from mean baseline to the third month, sixth month and final follow up period were calculated for the following metabolic parameters: HbA1C, weight, BMI, SBP, TC, HDL-C, LDL-C and TG-C. T sample T-test was used to compare statistical differences in the mean changes in the metabolic parameters in each group from baseline to follow up period. All data management and statistical analyses were conducted with MiniTab version 14. A p-value of less than 0.05 is considered statistically significant.

Results

Among the 188 study subjects included in our study between ages 20 to 88 years with mean age of 60, the predominant gender was female (n=132, 70%). African American makes up the majority (n=74, 39%), followed by Asian (n=40, 21%), Caucasian (n=34, 18%), Hispanic (n=22, 12%) and Indian (n=18, 10%). Majority of our patients with DM have concurrent hypertension (91%), hyperlipidemia (90%), and obesity (47%). See Table 1 for baseline demographics.

The group analysis showed that the DE group had a statistically significant decrease in mean HbA1C (mean change: -0.78%, p=0.013), TC (mean change: -16.89 mg/dL, p=0.01) and LDL-C (mean change: -11.75 mg/dL, p=0.04) from baseline to final follow up (see Table 2). The DE group had non-significant mean weight gain of 2.17 pounds and BMI of 0.52 kg/m^2.

Although DE+PS group were observed to have decreased in mean HbA1C (-0.48%), weight (-0.38 pounds), SBP (-3.24 mmHg), TC (-4.43 mg/dL) and TG-C (-12.89 mg/dL) and increased in HDL-C (+095 mg/dL), they were not statistically significant from initial to final follow up period. There were greater improvements in HbA1C and SBP from baseline to final follow up in DE+PS group compared to the control group. Only the control and DE+PS groups showed a decrease in weight from initial to final follow up.

Between the two intervention arms, the DE group exhibited greater reduction compared to DE+PS group in mean HbA1C (-0.78 vs. -0.48%), SBP (-3.78 vs. -3.24 mmHg), TC (-16.89 vs. -4.43 mg/dL), LDL-C (-11.75 vs. +0.08 mg/dL) and TG-C (-14.75 vs. -12.89 mg/dL).

Discussion

Our results suggested that among patients with DM, the subjects who participated in DE exhibited significant reduction in baseline HbA1C, TC and LDL-C compared to control. Furthermore, the significant impact of DE alone on optimizing control of HbA1C and LDL-C appeared to persist through time. In addition patients who received DE+PS also demonstrated moderate improvement in HbA1C, SBP, TC and TG-C and HDL-C even though they were not statistically significant on final follow up. It must be noted that the baseline mean HbA1Cs were higher in both interventions DE and DE+PS groups compared to control group and this may be associated with greater reduction in HbA1C in the intervention groups and may skew the finding. Our study results showed that DE group had greater percentage reduction in HbA1C (9%) compared to DE+PS group (5%) from baseline to the first follow up. The average change in HbA1C and LDL-C levels recorded in our study is similar to what has been reported in a previous study which showed significantly greater improvement in mean glycaemic levels and LDL-C levels in patients who participated in DE.[10]

However our findings are in stark contrast to a previous study that showed that DE+PS intervention has led to substantially greater weight reduction and improvement in HbA1C at second month post-intervention compared to education and control group.[15] This difference may be accounted for by the

Table 1. Baseline demographic characteristics of the study population

	Control [C] N=62	Diabetes Education [DE] N=63	Diabetes Education + Peer support [DE+PS] N=63
Baseline Characteristics			
Age range (years) [median]	32-76 [61]	20-88 [58]	26-86 [62]
Sex-male [N (%)]	22 (35)	20 (32)	14 (22)
Race			
African American	31 (50)	26 (41)	17 (27)
White	11 (17)	23 (37)	0 (0)
Indian	18 (29)	0 (0)	0 (0)
Asian	1 (2)	10 (16)	29 (46)
Hispanic	1 (2)	4 (6)	17 (27)
Comorbidities [N (%)]			
Hypertension[#]	54 (87)	59 (94)	58 (92)
Hyperlipidemia[¥]	56 (90)	61 (97)	53 (84)
Obesity*	29 (47)	29 (46)	31 (49)
Active cigarette smoker	6 (10)	5 (8)	1 (2)

[#] Hypertension is defined as mean systolic blood pressure > 140 mmHg and/or diastolic > 90 mmHg measured on two separate occasions. These patients have either hypertension diagnosed prior to or after diagnosis of DM.

[¥] Hyperlipidemia is defined as LDL > 100 mg/dl in patients with diabetes and diagnosis hyperlipidemia could be before or after diagnosis of DM.

* Obesity is defined as body mass index (BMI) of at least 30 kg/m^2 or greater.

Table 2. Mean Difference Scores and Confidence Interval for Metabolic Parameters from for Control, Education and Education + Peer support groups at 3 months, 6 months and final follow up*

Parameters	Mean (SD) at baseline	Change from baseline (95% CI) at 3 months	*P value*	Change from baseline (95% CI) at 6 months	*P value*	Change from baseline (95% CI) at Final follow up	*P-value*
HBA1C (%)							
C	7.5 (1.68)	0.0 (-2.06,2.07)	0.99	-0.33 (-0.91,0.24)	0.26	-0.28 (-0.37,0.93)	0.40
DE	9.3 (1.97)	-0.84 (-1.47,0.21)	**0.009**	-0.93 (-1.57,0.31)	**0.004**	-0.78 (-1.39,0.17)	**0.01**
DE+PS	8.3 (1.93)	-0.43 (-1.10,0.25)	0.213	-0.21 (-0.44,0.86)	0.52	-0.48 (-1.09,0.12)	0.11
Weight (lbs)							
C	182 (39.4)	+0.20 (14.59,14.18)	0.98	-0.24 (-14.13,14.62)	0.98	-0.59 (-13.49,14.69)	0.93
DE	173 (30.3)	+1.53 (-12.77,9.70)	0.79	+1.17 (-12.25,9.90)	0.83	+2.17 (-13.49,9.14)	0.70
DE+PS	183 (40.7)	-2.29 (-12.93,17.52)	0.77	+1.51 (-15.92,12.90)	0.84	-0.38 (-14.05,14.81)	0.96
BMI (kg/m2)							
C	30 (5.78)	-0.12 (-0.49,0.72)	0.71	-0.01 (-2.08, 2,11)	0.99	-0.11 (-1.94,2.16)	0.91
DE	30 (4.82)	-0.13 (-1.57,1.83)	0.88	+0.41 (-2.20,1.38)	0.65	+0.52 (-2.38,1.33)	0.58
DE+PS	32 (7.36)	-0.21 (-2.52,2.94)	0.88	+0.49 (-3.08,2.10)	0.70	+0.13 (-2.72,2.46)	0.92
SBP (mmHg)							
C	136 (16.1)	-1.29 (-5.11,7.69)	0.69	-6.91 (-12.9,0.93)	**0.02**	-1.61 (-4.57,7.79)	0.61
DE	139 (19.8)	-0.43 (-6.89,7.75)	0.91	-1.73 (-5.28,8.74)	0.63	-3.78 (-10.94,3.38)	0.30
DE+PS	131 (40.7)	+0.39 (-7.40,6.62)	0.91	-2.83 (-3.43,9.08)	0.37	-3.24 (-9.32,2.85)	0.29
TCH (mg/dL)							
C	174 (42.3)	-13.62 (-28.26,1.01)	0.07	-8.41 (-22.64,5.82)	0.24	-10.27 (-25.71,5.16)	0.19
DE	164 (39.5)	-18.81 (-32.03,5.59)	**0.006**	-12.60 (-26.26,1.06)	0.07	-16.89 (-26.68,4.09)	**0.01**
DE+PS	157 (42.7)	-4.11 (-12.43,20.66)	0.62	+2.76 (-17.95,12.43)	0.72	-4.43 (-10.35,19.21)	0.55
HDL (mg/dL)							
C	43 (12.4)	-0.22 (-4.43,4.88)	0.92	+1.20 (5.92,3.52)	0.61	+1.06 (-5.54,3.41)	0.64
DE	43 (10.6)	-1.69 (-5.77,2.38)	0.41	+1.05 (-5.31, 3.21)	0.63	-1.01 (-2.69,4.72)	0.59
DE+PS	45 (18.6)	-2.10 (-4.13,8.32)	0.51	-1.41 (-4.30,7.12)	0.62	+0.95 (-7.55,5.64)	0.78
LDL (mg/dL)							
C	101 (35.4)	-7.86 (-20.72,4.99)	0.23	-3.17 (-9.28,15.62)	0.61	-4.38 (-8.91,17.68)	0.52
DE	98 (32.5)	-13.84 (-25.13,2.55)	**0.017**	-12.46 (-23.42,1.51)	**0.03**	-11.75 (0.54,22.96)	**0.04**
DE+PS	91 (39.6)	-0.11 (-14.42,14.65)	0.99	+7.37 (-24.04,9.30)	0.38	+0.08 (-13.75,13.59)	0.99
TG-C (mg/dL)							
C	136 (84.3)	-17.65 (-43.70,8.39)	0.18	-21.73 (-48.99,5.53)	0.12	-18.11 (-44.66,8.43)	0.18
DE	117 (59.0)	-8.84 (-27.44,9.77)	0.35	-1.43 (-17.79,20.65)	0.88	-14.75 (-32.53,3.03)	0.10
DE+PS	112 (62.4)	-13.90 (-37.43,9.63)	0.24	-3.27 (-21.03,27.57)	0.79	-12.89 (-31.87,6.09)	0.18

* Final follow up varies for the three groups. 8 months for control (C), 13 months for education (DE) group and 19 months for education plus peer support (DE+PS) group

effect of sample size and the duration of follow up. The DE+PS group in our study included twice the number of patients being sampled compared to previous study (63 patients vs. 32 patients), and longer duration of follow up (19 months vs. 4 months)[15]. These differences are significant as they can influence the data trend.

In general, all groups had improvement in HbA1C, TC, TG-C levels, and SBP (though not significant). Only control and DE+PS groups had weight reduction and DE group had weight increase. Although the DE+PS group had improvement in most of the metabolic parameters they were not statistically significant throughout the entire follow up period compared to DE group. This scenario might be attributed to retrospective nature of the study, possible non-compliance of patients to medications, differences in duration of follow up between groups, and limited number of patients sampled thus hindering the appreciation of potential significant effect. The statistically significant differences in baseline HB A1C among the three groups could also explain the differing magnitude of change from baseline; DE group had higher baseline HbA1C compared to control group (9.3 vs. 7.5%; p=0.00) allowing for a greater change from baseline value. Similarly in DE+PS group, baseline HbA1C was considered statistically significant compared to control group (8.3 vs. 7.5%, p=0.018).

A previous randomized controlled trial assessing the effect of peer support on patients with type 2 diabetes with a 2-year follow up demonstrated no significant differences in HbA1C (-0.08%, 95% CI -0.35% to 0.18%), SBP (-3.9 mmHg, -8.9 to 1.1 mmHg) and TC (-0.03 mmol/l, -0.28 to 0.22 mmol/l).[16] It was suggested that the effect of DSM education on glycaemic control is greatest in the short-term and progressively attenuated over time and this may suggest that learned behaviour changes with time.[17,18] However, the result of the present study showed a persistently significant beneficial effect on HbA1C and LDL-C from the earliest follow up until the final month for patients receiving DE alone.

Previous meta-analysis of randomized trials of DSM education programs by Norris and colleagues (2002) demonstrated the beneficial effect of DE with estimated effect on glycaemic control (HbA1C) at -0.76% (95% CI: 0.34,1.18) compared to control immediately after the intervention.[17] However, the findings of the present study on the effect of peer education are in direct contrast with the results of the randomized trial using the Project Dulce model of peer-led education showing significant improvement from baseline to the tenth month of follow-up in HB A1C (-1.5%, p=0.01), TC (-7.2 mg/dl, p=0.04), HDL-C (+1.6 mg/dl, p=0.01) and LDL-C (-8.1 mg/dl, p=0.02).[19] This could be accounted for the different baseline values of the metabolic parameters in the present study, thus creating a bias in the magnitude of change.

It has been suggested that the most effective peer support model includes both peer support and a structured educational program. The emphasis on peer support is based on the recognition that people living with chronic illness can share their knowledge and experiences to one another.[20] It has been observed that participants in peer support groups were not interested in the topic of diabetes itself but on the effect and meaning of the disease on the lives of the patients.[21]

There are a number of limitations to be taken into consideration when interpreting the results of our study. Since our study is a retrospective review of medical records, the data collection was limited to availability of the required clinical data. Some parameters were not possible to obtain on a consistently uniform time frame. This resulted in varying mean duration for the 3 study groups (8 months for control group, 13 months for DE and 19 months DE+PS group). Because of unavailability of some of the clinical parameters at a specific time frame, there were variables missing on the earlier follow-ups. Our study also examined the effect of the intervention over a relatively short time. A longer-term study is necessary to determine if the intervention has lasting impact on improving the metabolic parameters, uplifting the quality of life and preventing morbidity and mortality from diabetes. The limited sample size could also be important factor that may influence the generalizability of the data. The differing baseline values in the metabolic parameters could have blunted the appreciation of possible significant improvement in the metabolic parameters in the DE+PS group. Other confounding factors that were not analysed in the present study and could have affected the results include the use of insulin regimen among the different groups, initiation of additional oral hypoglycemic agents, medication adherence by the patients and adjustment by physicians, and whether the patients were seen by endocrinologists or not.

The present study suggested that participation in DE may assist with optimizing HbA1C, TC and LDL-C. The DE group had improvement in glycaemic control and other metabolic parameters. The significant metabolic improvement gained from DE appeared to be sustained over time. However, participation in both DE+PS showed relative improvement but not significant as it is likely due to confounding different baseline metabolic parameter and duration being compared. Our findings underscore the importance of DE as part of the treatment plan for patients with DM. The addition of peer support group may or may not contribute to significant improvement of metabolic parameters.

Acknowledgements
The authors would like to extend their gratitude to: Nayab Bakshi, Edan Elias and Dorota Pazdrowska for assistance on data recording.
Competing Interests
None declared
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REFERENCES

1. Centres for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011[Internet]. Atlanta (GA);2011. Available from: http//www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
2. Boyle JP, Thompson TJ, Gregg EW, et al. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modelling of incidence, mortality and prediabetes prevalence. Popul Health Metr. 2010; 8:29.
3. S. Wild, G Roglic, A. Green, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27 (5);2004; 1047-1053.
4. American Diabetes Association. Standards of medical care for patients with diabetes mellitus (position statement). Diabetes Care 2001;24 (Suppl 1):S33-43.
5. Healthy People.gov. Healthy People 2020:goals and objectives-diabetes [Internet]. Washington (DC):Department of Health and Human Services; 2011. Available from: http://healthypeople.gov/2020/topicsobjectives 2020/overview.aspx?topicid=8.
6. American Diabetes Association. Standards of medical care in diabetes-2011. Diabetes Care. 2011;34 (Suppl 1):S11-8
7. Gaede P, Lund-Andersen H, PArving H-H, et al. Effect of multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580-591.
8. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death and microvascular events in type 2 diabetes: meta-analysis of randomized controlled trials. BMJ 2011;343:d4169.
9. Stratton IM, Adler AI, Neil JA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35):prospective observational study. BMJ 2000;321(7258):405-12.
10. Roblin DW, Ntekop E, Becker ER. Improved intermediate clinical outcomes from participation in a diabetes health education program. J Ambulatory Care Manage 2007; 30(1);64-73.
11. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA 2002a. 288(14), 1775-1779.
12. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness:the chronic care model, part 2. JAMA 2002b, 288(15),1909-1914.
13. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Quarterly 1996, 74(4), 511-544.
14. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes. A systematic review of randomized controlled trials. Diabetes Care 2011, 24(3),561-587.
15. Wilson W. Pratt C. The impact of diabetes education and peer support upon weight and glycaemic control of elderly persons with noninsulin dependent diabetes mellitus (NIDDM).Am J Public Health May 1987; 77(5),634-635.
16. Smith SM, Paul G, Kelly A, Whitford DL, et al. Peer support for patients with type 2 diabetes: cluster randomized controlled trial. BMJ 2011;342:d715.
17. Norris SL, Lau JS, Schmid CH, et al. Self-management education for adults with type 2 diabetes: A meta-analysis of the effect on glycaemic control. Diabetes Care 2002; 25(7),1159-1171.
18. Brown S. Meta-analysis of diabetes patient education research: variation in intervention effects across studies. Res Nurs Health 1992;15:409-419.
19. Philis-Tsimikas A, Fortmann A, Lleva-Ocana L, et al. Peer-led diabetes education programs in high-risk Mexican Americans improve glycaemic control compared with standard approaches. Diabetes Care 2011;34:1926-1931.
20. Heisler M. Overview of peer support models to improve diabetes self-management and clinical outcomes. Diabetes Spectrum 2007;20(4):214-221.
21. Rugh D. Design of a rural diabetes self-directed care program. Soc Work Health Care 2011;50(10):775-786.

Research Article

BJMP 2013;6(4):a632

Daycase Anterior Cruciate Ligament Reconstruction: Success, Pitfalls and Patient Pain Scores

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Abstract

Daycase Anterior Cruciate Ligament (ACL) reconstructions with hamstring autograft have been undertaken in this trust for the last 6 months. Performing the procedure as a daycase potentially reduces the risk of infection and cancellation as well as reaching government targets for the performance of at least 75% of all surgical procedures as a daycase.

We analysed our attempted daycase ACL reconstructions between April 2009 and October 2009. We assessed success of the daycase discharge as well as reasons for failed discharge. Patients' pain scores were assessed for the week post-surgery and patient satisfaction with the daycase procedure was also documented.

Daycase ACL reconstructions were attempted in 50 patients. Average age was 31.0 years and there were 36 males and 14 females in the cohort. 29 patients were discharged as a daycase and 21 patients required inpatient stay (38% social reasons, 33% late back to ward, 10% due to pain, 10% dues to dizziness and 10% due to failed physiotherapist assessment)

Patients having daycase ACL reconstructions have significantly less pain from days 1-3 post-operatively ($p=0.05$) compared to inpatients. There is no significant difference ($p=0.05$) between different nerve blocks used (Femoral vs Femoral and Sciatic). No correlation was noted between increased pain and additional procedures performed at the time of the ACL reconstruction.

100% of patients claiming they were happy with the daycase procedure and 96.6% would agree to have the procedure performed as a daycase again.

New protocol has been devised to allow daycase ACL reconstructions to be performed only in the mornings. Anaesthetic has been standardised with General anaesthetic and only femoral nerve block. Re-audit has shown that the majority of patients are now discharged as a daycase and patient outcome is improved.

We conclude that daycase ACL reconstruction does not cause significantly increased pain and grants excellent patient satisfaction. There is no apparent difference in pain scores between patients having femoral nerve blocks and those having sciatic blocks added in. The procedure is safe and efficient and will continue to be offered in the trust.

Keywords: Daycase, Cruciate, Ligament, Reconstruction, Pain, Satisfaction

Introduction

Anterior Cruciate Ligament (ACL) reconstructions are increasingly being undertaken throughout the United Kingdom (UK). Advances in General and Local Anaesthetic as well as surgical technique allow reconstructions as a day case procedure.[1,2,3] There are currently no studies showing post-operative pain suffered by ACL reconstruction patients, nor showing the comparison of day case and inpatient pain scores.

We document, prospectively, patients' post-operative pain after ACL reconstructions. We aim to identify and assess factors that affect pain post-ACL reconstructions including additional procedures, type of nerve blocks and whether the procedure was performed as a day case or as an inpatient.

We propose that patients having ACL reconstruction have no difference in pain scores when having the procedure as a day case compared to performance with inpatient stay. We also propose that additional procedures do not cause an increase in pain. We hypothesise that patients having Femoral nerve block have no increase in pain compared to patients having combined Femoral and Sciatic nerve block.

Method

All patients having ACL reconstruction between April 2010 and September 2010 were evaluated prospectively. Four strand arthroscopic hamstring reconstructions were performed by two specialist knee surgeons using a similar technique. Anaesthetic was performed by varying anaesthetists with a General Anaesthetic and Regional Nerve Block with Bupivicaine (Femoral nerve block or Femoral plus Sciatic nerve block). This was performed in the anaesthetic room under ultrasound guidance. Intra-operatively, patients received standardised anaesthesia. All patients received one dose of intravenous Paracetamol and two intravenous doses of opiates (Morphine or Fentanyl, as tolerated) at the beginning and end of the procedure.

Inclusion criteria used were all ACL reconstructions performed on patients over 16 years of age. No exclusion criteria were used.

Arthroscopic hamstring reconstruction was undertaken using a four strand Semitendinosus and Gracilis graft. During the arthroscopy, any additional procedures necessary were performed (e.g. meniscal repair, menisectomy, etc.). No drains were used. The knee was placed into an immobilisation splint until the nerve blocks had worn off.

Patients were discharged once they were back on the ward and deemed safe for discharge by the physiotherapists, medical and nursing staff. They were discharged with Paracetamol, a non-steroidal anti-inflammatory (if tolerated) and a mild opiate (Tramadol or Codeine Phosphate).

After discharge from the ward, patients were brought back to an aftercare clinic, with a senior physiotherapist, any time up to 48 hours post-operatively, to assess whether the nerve block had worn off, perform a wound check and to reinforce physiotherapy advice.

Patients were given a discharge questionnaire asking them to record their pain scores daily, when the pain was at its worst, using the Numerical Rating Scale (NRS) from 0-10. Documentation commenced on the day of the procedure and was requested daily for one week. Complications were also documented by the patient. These questionnaires were handed in at the two week follow up appointment, at which point patients were also asked if they would have the surgery performed as a day case again.

Pain scores were analysed using a Box-whisker plot followed by a Shapiro-Wilk W test which showed a non-parametric data spread. Scores were subsequently analysed using a Mann-Whitney U test to assess significance (p=0.05).

Results

ACL Reconstruction was attempted in 50 patients from April 2009 up to and including September 2009. The average age of patients was 31.0 years (Range 16-55). Of the cohort, there were 36 male patients with 14 females. All of the ACL reconstructions had a General Anaesthetic and all had infiltration of their graft site and medial wound with Bupivicaine. 42 had a Femoral nerve block with Bupivicaine and eight had a Bupivicaine Femoral and Sciatic nerve block. Of the 50 patients, 13 patients had additional procedures formed.

29 patients from the group were discharged as a day case. 21 patients required inpatient stay for the reasons documented in Figure 1 below.

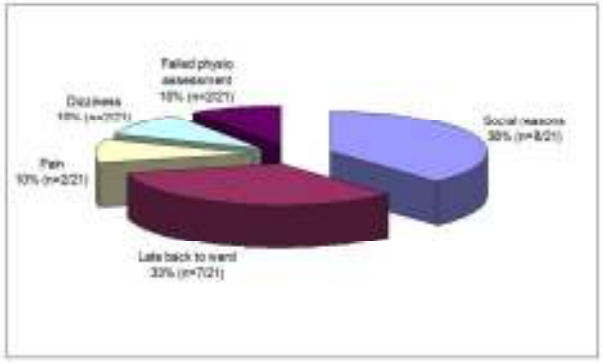

Figure 1. Reasons for inpatient stay after ACL reconstruction

Social reasons for inpatient stay included out-of-area patients and those who had no home support to care for them on the day of surgery. Patients who were unable to safely mobilise post-operatively were classified as having failed physiotherapist discharge assessment. Two patients were unable to be discharged due to excessive pain. Two patients had symptoms related to General Anaesthesia (e.g. nausea and dizziness) which prohibited discharge. Seven patients arrived back onto the ward with insufficient time for recovery and physiotherapy assessment, thus preventing day case discharge. In all seven cases, this was due to ACL reconstruction being performed late on the operating list.

On day one post-operatively the average NRS pain score for the day case group was 4.1, the average score for the inpatient group was 5.52. The pain score decreased steadily as the week went on. Pain scores on days one to four was statistically lower (p=0.05) in day case patients compared to inpatients (Table 1 and Figure 2). Figures 3 and 4 show the box whisker plots for inpatient vs day case pain scores on day 1 and 2.

Post-operative day	Daycase Pain Score (N1=29)	Inpatient Pain Score (N2=21)	P Value (*=significant)
1	4.1	5.52	0.03*
2	3.93	5.14	0.04*
3	3.62	4.81	0.03*
4	3.1	4.38	0.03*
5	3.1	4.29	0.09
6	2.69	4.00	0.03*
7	2.52	3.62	0.06

Table 1. Average NRS pain scores of patients undergoing ACL reconstruction

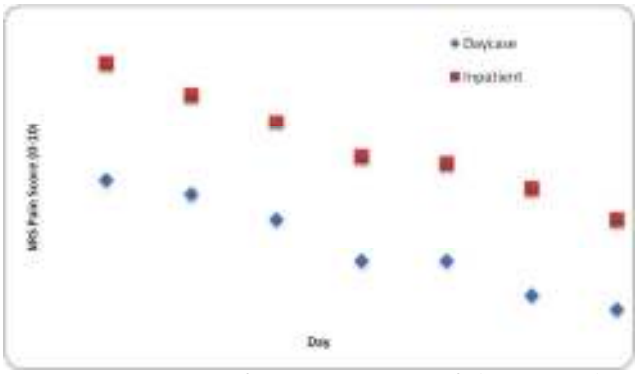

Figure 2. Comparison of NRS pain scores of day case and inpatient ACL reconstruction

Out of 50 patients, 42 patients had Femoral nerve blocks with the remaining eight patients having a combined Femoral and Sciatic nerve block. On average, patients receiving only a Femoral nerve block had lower pain scores compared to those receiving the combined block, although with the difference in cohort numbers, there was no statistical difference (p=0.09 on day 1 and p=0.5 on day 2) [Figure 5].

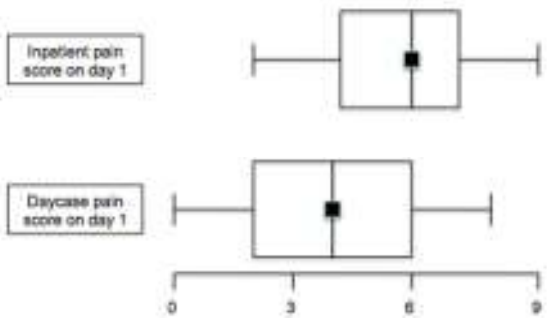

Figure 3. Box Whisker plots for pain scores on day 1 for inpatients and day case patients

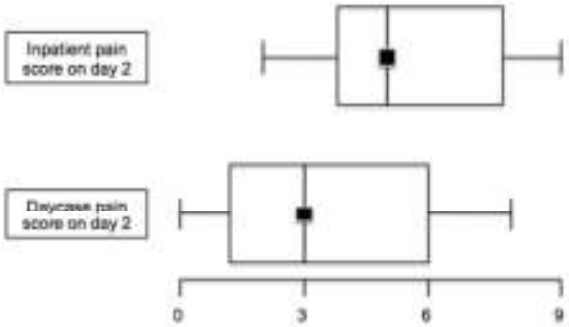

Figure 4. Box Whisker plots for pain scores on day 2 for inpatients and day case patients

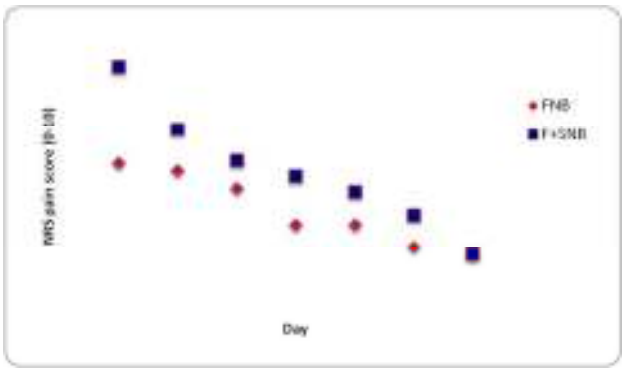

Figure 5. Comparison of daily pain scores with Femoral and Femoral/Sciatic nerve blocks

Of the 50 patients attempting the day case procedure, there were 17 additional procedures. Eight partial medial menisectomies, three partial lateral menisectomies, two lateral meniscal repairs, two medial meniscal repairs and two medial femoral condyle microfractures. There was no correlation identified between additional procedures and increased patient pain scores (Figure 6).

When patient satisfaction among the 29 patients who had day case ACL reconstruction was asked, 100% were happy with the day case procedure. One patient felt that they would opt to have the operation done with an inpatient stay as they felt "groggy" overnight. They were otherwise happy with the day case procedure.

All patients had quadriceps function return at day 1 post-operatively and there were no re-admissions due to pain or being unable to cope at home. There were no infections amongst the groups.

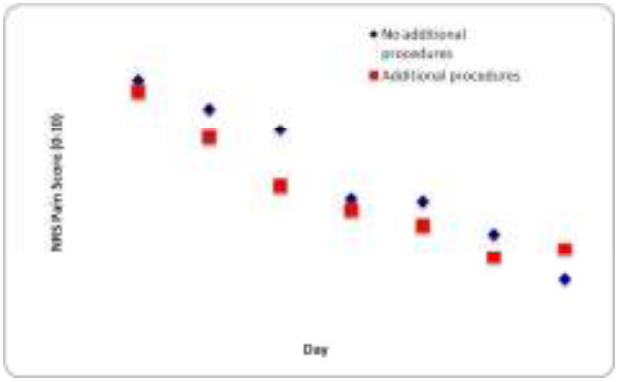

Figure 6. Comparison of pain scores of patients having additional procedures

Discussion

Day case ACL reconstructions are commonly undertaken in the UK. Literature from Sheffield, Glasgow and Romford[1,2,3] shows that the rate of admission and complications is low and the procedure is safe and effective. It has been well tolerated by patients.

Day case surgery is encouraged by the government led Department of Health.[3,4,5] It reduces the risk of cancellations and infections and can also have economic benefits for the National Health Service (NHS). In the United States (US), Bonsell has shown that a single day case ACL reconstruction saves the hospital $2234 compared to a procedure with an inpatient stay. Bonsell also proposed that day case ACL reconstructions are performed significantly quicker than inpatient reconstructions (approximately 23 minutes quicker) which could save the hospital $85000 per year.[6]

Day case patients were found to have statistically significant, lower pain scores compared to inpatients. Farrar et al have shown that, using the NRS pain scoring system, only a difference of greater than two points can be deemed clinically significant. However, the results of this study have shown that there is no clinical difference or worse pain when the procedure is performed as a day case.[7] Krywulak et al noted that the average Visual Analogue Score (VAS) score for patients' satisfaction post-day case ACL reconstructions was 85.1 compared to the inpatient average score of 78.2.[8]This is validated in our study of which 100% of patients were happy with the day case procedure.

Patients were encouraged to take analgesia regularly for two weeks post-operatively but the amount of medication actually taken was not formally documented. This could potentially lead to some of the bias in this study. However, the significance of this bias is difficult to determine accurately as the NRS pain scores were recorded when the patients' pain was at its worst. This would most likely be between analgesic doses so hopefully eliminating some of the bias.

Little is known about pain associated with the procedure of day case ACL reconstruction and also pain suffered compared to those undergoing inpatient stay. We have been able to compare pain scores of patients undergoing ACL reconstruction as a day case procedure with those undergoing the procedure as an inpatient. We found that patients having the procedure as a day case had significantly lower pain scores on days 1-4 post-ACL reconstruction compared to inpatients.

Day case ACL reconstructions are safe and not associated with any difference in pain compared to inpatient stays. This is important in pre-operative guidance given to patients and, in view of the risks of hospital inpatient stays and also additional costs to the Health Service and Primary Care Trust (PCT), ACL reconstruction as a day case procedure should be highly recommended to patients compared to an inpatient surgical procedure.[9-11] Information can be given to patients advising them that pain will not be worse when the procedure is performed as a day case which will encourage more patients to accept same day discharge.

Further work needs to be done to assess the possible difference in pain scores associated with Femoral nerve blocks compared with combined Femoral and Sciatic nerve blocks but our results appear to show that significant difference is unlikely.

Patient satisfaction with the day case ACL procedure was excellent and subsequently day case ACL reconstruction is now routinely performed in this Trust.

Competing Interests
None declared
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REFERENCES

1. Shaw AD, DiBartolo G, Clatworthy M. Daystay hamstring ACL reconstruction performed under regional anaesthesia. Knee. 2005; 12: 271-273
2. Talwalker S, Kambhampati S, De Villiers S, booth R, Lang-Stevenson. Day case Anterior Cruciate Ligament Reconstruction: A study of 51 consecutive patients. Acta Orthopaedica Belgica. 2005; 71:309-314
3. Kumar A, Bickerstaff DR, Johnson TR, Appleton DFJ. Day surgery anterior cruciate ligament reconstruction: Sheffield experiences. Knee. 2001; 8: 25-27
4. Kao JT, Giangarra CE, Singer G, Martin S. A comparison of outpatient and inpatient anterior cruciate ligament reconstruction surgery. Arthroscopy 1995; 11: 151–6.
5. Department of Health. Day Surgery: Operational Guide. August 2002 www.dh.gov.uk
6. Bonsell SW. Financial analysis of anterior cruciate ligament reconstruction at Baylor University Medical Center. Proceedings (Baylor University Medical Center). 2000; 13(4):327-330
7. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2005; 94(2):149-158
8. Krywulak Sa, Mohtadi NG, Russell ML, Sasyniuk TM. Patient satisfaction with inpatient versus outpatient reconstruction of the anterior cruciate ligament: a randomized clinical trial. Canadian Journal of Surgery. 2005; 48(3):201-206
9. Acute hospital portfolio – review of national findings. Day Surgery Audit Commission 2001
10. Day surgery – Report by the Day Surgery Task Force. NHS Management Executive (Department of Health) September 1993
11. A short cut to better services – Day surgery in England and Wales Audit Commission 1990

Research Article

BJMP 2013;6(4):a628

Effects on hepatic and renal biomarkers in patients of colorectal carcinoma treated with two different schedules of 5FU/LV

Nusrat Bano, Rahila Najam and Ahmed Mateen

Abstract
5 Fluorouracil with leucovorin is the mainstay in the treatment of colorectal carcinoma (CRC), the third leading cause of cancer related deaths. Aims: This study is designed to assess the effects of 5FU and leucovorin chemotherapy (in continuous and intermittent schedules) on the serum biomarkers indicative of hepatic and renal functions.
Methods: Biochemical profiles of patients comprising of age group 61.0 + 4.58, with histologically confirmed colorectal carcinoma, treated either with de Gramont's regimen or Mayo clinic regimen were assessed after each alternate cycle of treatment. The changes in the levels of hepatic enzymes (ALT, AST, bilirubin, $AlkPo_4$, TGS) and renal biomarkers (serum creatinine, BUN) were comparatively assessed with the pretreatment values. Results: Changes in the serum creatinine levels from pretreatment value was significant after fourth cycle of treatment (p=0.035). Changes in AST levels were significant after the second cycle of treatment (p= 0.049) and very significant after fourth cycle of treatment (p=0.008). Conclusion: A gradual rise in mean values is assessed for serum creatinine and BUN levels indicative of progressive decline in renal functional status. Hepatic enzyme elevation is pertinent to cumulative dose intensity.
Keywords: 5Fluorouracil, Colorectal Carcinoma, Creatinine, BUN, Hepatic enzymes

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women worldwide (1) and a leading cause of cancer related deaths (2). 5FU synthesized in 1957 by Heidelberger (3) is the mainstay in all current standard regimens for CRC (4). Chemotherapy induced hepatic toxicity in 5FU based regimens can be an acute or delayed outcome (5, 6); whereas steatosis is a hallmark of 5FU induced hepatic toxicity (7). Chemotherapy induced nephrotoxicity (8) is also an area of concern for oncologists. The antimetabolite 5FU is often linked with kidney damage (9). Therapeutic outcomes and toxicity of 5FU differs markedly in different doses, combinations, schedules of administration and routes of administration. Leucovorin (LV) incorporated in 5FU based regimen enhances the cytotoxicity of 5FU. In this study we opt to report abnormalities in hepatic enzymes and renal biomarkers biochemically assessed in the serum after alternate cycles of treatment in CRC patients subjected to 5FU/LV based chemotherapy.

Methods

The study was designed in the Department of Pharmacology, University of Karachia and conducted in a leading cancer hospital in Pakistan. Following institutional authorisation, informed consent was obtained from patients being admitted during 2008-2011. The inclusion criterion was maintained on the following grounds:

1. Histologically confirmed advanced colorectal carcinoma
2. Adequate blood count before therapy
3. Age 20-80 years
4. ECOG score of ≤ 3
5. Serum bilirubin $\leq 5\times$ normal
6. Serum creatinine $\leq$ 135µmol/liter
7. Serum transaminases $\leq \times 2.5$ normal

Twenty three patients (median age 59 years) who underwent surgery were included in the study. All the patients had measureable disease at CT scan, ultrasonography or clinical examination. Patient's characteristics are shown in Table 1. Seventeen patients were treated with the adjuvant bimonthly regimen of 5FU/LV - high dose Folinic acid (de Gramont Regimen); whereas, six patients were treated with adjuvant monthly regimen of 5FU/LV –low dose Folinic acid(Mayo Clinic Regimen) as follows.

5Fluorouracil/ Leucovorin (*de Gramont's regimen*)
5Fluorouracil: 400mg/m^2 IV followed by 600mg/m^2 CIV for 22 hours on day 1-2.
Leucovorin: 600 mg/m^2 IV as 2 hours infusion before 5FU on day 1-2.
Cycle repeated after 2 weeks.

5Fluorouracil/ Leucovorin (*Mayo clinic regimen*)
5Fluorouracil: 425mg/m^2 IV on day 1-5.
Leucovorin: 20 mg/m^2 IV before 5FU on day 1-5.
Cycle repeated after 4-5 weeks.

Premedication with oral phenothiazines, $5HT_3RA$ and 10-20 mg of dexamethasone was given.

The blood samples were collected before the initiation of the therapy and after each alternate cycle of treatment. The blood was drawn when the patient was rested and comfortable from the antecubital vein under minimal tourniquet pressure. The blood drawn was sampled and collected into vacutainers (BD). The biochemical profile of the pretreatment and subsequent

treatment was comparatively assessed. SGOT, SGPT, bilirubin and alkaline phosphatase levels were measured after each cycle of treatment or on the clinical presentation of any hepatic adverse effect notified by the physician or oncologist and the levels were compared to the pretreatment values. The serum creatinine levels and BUN was measured before the start of chemotherapy and after each alternate cycle of treatment up to six times in each patient.

Table 1 Patient characteristics

Parameters	Arm A de Gramont		Arm B Mayo Clinic	
	No. of Patients	%	No. of Patients	%
Demographic Characteristics				
Male	12	70.58	4	66.6
Female	5	29.41	2	33.3
Total Patients	17		6	
Age: Years				
Median	59			
Range	56-65			
ECOG Performance Status (21)				
0	1	5.88	1	16.6
1	3	17.64	1	16.6
2	13	76.47	4	66.6
3	0	0	0	0
Primary Site				
Colon	11	64.7	3	50
Rectum	5	29.4	2	32.3
Multiple	1	5.88	1	16.6
Metastases				
Synchronous	11	64.7	4	66.6
Metachronous	6	35.2	2	32.3
Metastatic Site				
Liver	8	47.0	1	16.6
Lymph nodes	4	23.5	2	32.3
Other*	5	29.4	3	50
No. of Sites				
1	7	41.1	2	32.3
≥ 2	10	58.8	4	66.6
CEA				
< 10ng/ml	2	11.7	1	16.6
≥10ng/ml	8	47.0	1	16.6
Unknown	7	41.1	4	66.6
* = Peritoneal/ovary				

Results

Table 2shows that the SGOT levels are raised after each cycle of treatment and the difference between the SGOT levels of the patients before treatment and after subsequent cycle of

Table 2 Comparative changes in hepatic biomarkers in patients treated with 5FU/LV regimen

Paired Samples Test						
			Paired Differences		t	p-value
			Mean	Std. Deviation		
Hepatic	TGS	Control - Cycle 2	-1.200	1.643	-1.633	0.178
		Control - Cycle 4	-3.200	3.033	-2.359	0.078
		Control - Cycle 6	-3.400	2.966	-2.563	0.062
		Control - Cycle 8	-10.000	10.198	-2.193	0.093
		Control - Cycle 10	-3.600	8.414	-0.957	0.393
		Control - Cycle 12	-8.800	12.872	-1.529	0.201
	SGOT / AST	Control - Cycle 2	-12.667	5.033	-4.359	0.049
		Control - Cycle 4	-22.000	3.464	-11.000	0.008
		Control - Cycle 6	-22.667	3.055	-12.851	0.006
		Control - Cycle 8	-25.333	3.055	-14.363	0.005
		Control - Cycle 10	-27.000	7.810	-5.988	0.027
		Control - Cycle 12	-28.667	7.024	-7.069	0.019
	SGPT / ALT	Control - Cycle 2	-2.667	3.055	-1.512	0.270
		Control - Cycle 4	-3.667	2.082	-3.051	0.093
		Control - Cycle 6	-9.333	8.505	-1.901	0.198
		Control - Cycle 8	-12.667	8.083	-2.714	0.113
		Control - Cycle 10	-17.667	5.859	-5.222	0.035
		Control - Cycle 12	-22.667	10.214	-3.844	0.062
	Bilirubin	Control - Cycle 2	0.033	0.058	1.000	0.423
		Control - Cycle 4	0.000	0.100	0.000	1.000
		Control - Cycle 6	-0.267	0.058	-8.000	0.015
		Control - Cycle 8	-0.267	0.058	-8.000	0.015
		Control - Cycle 10	-0.267	0.058	-8.000	0.015
		Control - Cycle 12	-0.367	0.115	-5.500	0.032
	$ALKPO_4$	Control - Cycle 2	-6.667	5.774	-2.000	0.184

		Control - Cycle 4	-10.000	10.000	-1.732	0.225
		Control - Cycle 6	-26.667	11.547	-4.000	0.057
		Control - Cycle 8	-43.333	40.415	-1.857	0.204
		Control - Cycle 10	-60.000	36.056	-2.882	0.102
		Control - Cycle 12	-63.333	40.415	-2.714	0.113

treatment is significant in the patients treated with 5FU/LV (p value < 0.05). The difference in the SGPT levels of the patients from the pretreatment value is not highly significant (p value >0.05). The difference in the bilirubin levels of the patients after the sixth cycle of chemotherapy with 5FU/LV regimens is highly significant from the pretreatment level (p value < 0.05). The difference in the alkaline phosphatase levels of the patients after chemotherapy with the pretreatment value in the same patients is not significant (p value >0.05).The difference in the triglyceride levels is not significant before and after chemotherapy in the patients treated with 5FU/LV.

Table 3 Comparative changes in renal biomarkers in patients treated with 5FU/LV regimen

Paired Samples Test						
			Paired Differences		t	p-value
			Mean	Std. Deviation		
Renal	Creatinine	Control - Cycle 2	-0.120	0.130	-2.058	0.109
		Control - Cycle 4	-0.160	0.114	-3.138	0.035
		Control - Cycle 6	-0.242	0.204	-2.646	0.057
		Control - Cycle 8	-0.264	0.225	-2.627	0.058
		Control - Cycle 10	-0.546	0.422	-2.893	0.044
		Control - Cycle 12	-0.566	0.463	-2.734	0.052
	BUN	Control - Cycle 2	-1.800	1.924	-2.092	0.105
		Control - Cycle 4	-1.800	1.924	-2.092	0.105
		Control - Cycle 6	-2.000	2.449	-1.826	0.142
		Control - Cycle 8	-3.000	2.550	-2.631	0.058
		Control - Cycle 10	-4.400	4.037	-2.437	0.071
		Control - Cycle 12	-6.400	8.204	-1.744	0.156

Table 3 shows that the creatinine levels are raised in patients following each subsequent cycle of treatment with 5FU/LV regimens. The difference in the serum creatinine levels after the fourth and the tenth cycle of treatment with the pretreatment levels was significant ($p<0.05$). The difference in the BUN levels measures before and after chemotherapy with 5FU/LV was not significant following alternate cycles of treatment.

Discussion:

The hepatocellular enzyme findings are indicative of deteriorating liver function. The levels of SGOT and SGPT both differ from the control values and point toward 5FU induced hepatic toxicity. Increase in SGOT and SGPT up to grade 2 (CTC of NIC) is reported by Hotta and colleagues (10) in a study based on clinicopathological assessment of 36 patients treated with 5FU/LV. They did not report grade 3 or grade 4 elevations in SGOT and SGPT ratio. In our data there is considerable difference in SGOT levels (mean value) after the second cycle of treatment as compared to the pretreatment levels (mean value). Similarly SGPT levels are perturbed following treatment and the difference in the SGPT levels from the pretreatment control value is statistically significant after the tenth cycle of treatment. The pooled data of all the patients cannot be used for prognostic or diagnostic assessment; however, it shows a pattern of drug induced alterations in hepatic functions. An early effect on SGOT level show mild progressive damages correlated with a prominent rise in SGPT levels. SGOT is found in cytosol whereas SGPT is in mitochondria. Any mild to moderate damage to the hepatic cells will result in a rise in SGOT levels even though SGPT levels may remain normalised. Moderate to Severe hepatic damage will give a rise in both SGOT and SGPT elevation. SGOT is located in red blood cells, kidneys, brain, skeletal muscle and cardiac tissues; hence a prompt rise in SGOT level is indicative of associated damages. SGPT is present in skeletal muscles and cardiac tissues and the serum levels are affected with myocardial and skeletal muscle damages. Cytotoxic chemotherapy is frequently associated with fatty liver disease, chemical hepatitis and reactivation of hepatitis B (11). The elevation in triglyceride levels is indicative of drug induced steatosis (fat globule deposition in hepatocytes) leading to postoperative hepatic insufficiency(8). A significant change in bilirubin from the pretreatment level is observed after the 6^{th} cycle of treatment. Biliary changes are detectable and persistent since the drug is excreted in the bile. Sclerosing cholangitis with elevation in alkaline phosphatase and bilirubin levels secondary to 5FU plus mitomycin therapy is reported by Fukuzumi et al (12). After intravenous administration, 5FU is converted into its active form '5-fluoro-deoxyuridine-monophosphate' by anabolic reactions in the tissues. The drug undergoes catabolism primarily in the liver by reduction of the pyrimidine ring by enzymatic action of dihydrouracil dehydrogenase (13). The compound is then cleaved to urea, ammonia, carbondioxide and α-fluoro-β-alanine. The catabolic process in the liver amounts for 5FU induced hepatic toxicity. Hepatic and renal toxicity associated with 5FU is reported earlier with IV administration of 5FU (14). The risk of 5FU

induced hepatic damages is increased in older patients (15). Older patients included in our study with increased post-treatment transaminase levels were more frequently presented with pruritus and hand and foot syndrome.This complexity of the situation is that altered hepatic function increases the risk of 5FU concentration (since it is catabolized in the liver cells), which in turn adds to the hepatic damage.

Creatinine clearance and blood urea nitrogen (BUN) are conventional biomarkers of renal function for convenient and cost-effective assessment (16). A detectable change in the creatinine levels of the patients ensue after the fourth cycle of treatment. Besides suggesting a decline in the renal function, it also indicates defect in hepatic functional status and progressive cachexia (muscle wasting), both of which are readily assessed in the patients during treatment. BUN levels are also affected by dexamethasone pretreatment, dehydration and azotemia besides renal function. Nephrotoxicity with 5FU chemotherapy is usually reported when it is combined with cisplatin with worsened creatinine levels (17, 18). Tubular damage induced by 5FU plus high dose leucovorin chemotherapy (similar to de Gramont's regimen in our study) is reported by Kintzel, who also reported 50% decline in creatinine clearance in three patients (19). Chemotherapy induced renal damages are detected with abnormal creatinine and BUN levels, but in most cases the renal tubes remain intact and functional as the normal renal blood flow and GFR is reversibly attained (20). Adequate hydration and simultaneous treatment with mesna, which neutralises the toxic metabolites can effectively reduce chemotherapy induced renal damage (8).

Conclusion

SGOT and bilirubin levels are raised after each cycle of treatment and the difference between the SGOT levels of the patients treated with 5FU/LV, before treatment and after subsequent cycle of treatment are highly significant indicative of mild to moderate progressive hepatic toxicity. Risk of clinical and subclinical renal damage is observed by a subsequent rise in serum creatinine and BUN levels. Renal toxicity marked by creatinine elevation is prominent after the fourth cycle of treatment.

Competing Interests
None declared
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REFERENCES

1. 1.Dietvorst MH, Eskens FA. Current and Novel Treatment Options for Metastatic Colorectal Cancer: Emphasis on Aflibercept. Biologics in Therapy. 2013: 1-9.
2. 2.Sadanandam A, Lyssiotis CA, Homicsko K et.al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nature medicine.2013; 19(5): 619-625.
3. 3.Bano N, Najam R, Mateen A et.al. High and Low Dose Folinic Acid, 5-Fluorouracil Bolus and Continuous Infusion for Poor-Prognosis Patients with Advanced Colorectal Carcinoma. Asian Pacific Journal of Cancer Prevention.2012; 13: 3589-3593.
4. 4.Newton K F, Newman W, Hill J. Review of biomarkers in colorectal cancer. Colorectal Disease. 2012;14(1): 3-17.
5. 5.Masi G, Loupakis F, Pollina L et.al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Annals of surgery.2009; 249(3): 420-425.
6. 6.Khan A Z, Morris-Stiff G, Makuuchi M. Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. Journal of hepato-biliary-pancreatic surgery. 2009; 16(2): 137-144.
7. 7.Qi J, Fong Y, Saltz L.et.al. Serial measurement of hepatic lipids during chemotherapy in patients with colorectal cancer: a 1H MRS study. NMR Biomed. 2013; 26: 204–212.
8. 8.Torrisi J M, Schwartz LH, Gollub MJ et.al. CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology.2011; 258(1): 41-56.
9. 9.Rashid S, Ali N, Nafees S.et.al. Abrogation of 5-flourouracil induced renal toxicity by bee propolis via targeting oxidative stress and inflammation in Wistar rats. Journal of Pharmacy Research.2013.
10. 10.Hotta T, Takifuji K, Arii K. Clinical impact of adjuvant chemotherapy on patients with stage III colorectal cancer: l-LV/5FU chemotherapy as a modified RPMI regimen is an independent prognostic factor for survival. Anticancer research.2006; 26(2B): 1425-1432.
11. 11.Floyd J, Mirza I, Sachs B.et.al. Hepatotoxicity of chemotherapy. In Seminars in oncology. 2006; 33(1): 50-67.
12. 12.Fukuzumi S, Moriya Y, Makuuchi M. Serious chemical sclerosing cholangitis associated with hepatic arterial 5FU and MMC chemotherapy. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 1990; 16(3): 251.
13. 13.King P D, Perry MC. Hepatotoxicity of chemotherapy. The oncologist.2001;6(2): 162-176.
14. 14.Bateman JR, Pugh RP, Cassidy FR et.al. 5-fluorouracil given once weekly: Comparison of intravenous and oral administration. Cancer. 1971; 28(4): 907-913.
15. 15.Tesch GH. Review: Serum and urine biomarkers of kidney disease: A pathophysiological perspective. Nephrology. 2010; 15(6): 609-616.
16. 16.Welz S, Hehr T, Kollmannsberger C.et.al. Renal toxicity of adjuvant chemoradiotherapy with cisplatin in gastric cancer. International Journal of Radiation Oncology* Biology* Physics. 2007;69(5): 1429-1435.
17. 17.Ries F, Klastersky J. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. Am J Kidney Dis. 1986; 8(5): 368-379.
18. 18.Metz-Kurschel U, Kurschel E, Wagner K. et.al. Folate nephropathy occurring during cytotoxic chemotherapy with high-dose folinic acid and 5-fluorouracil. Renal failure. 1990;12(2): 93-97.
19. 19.Kintzel PE. Anticancer drug—induced kidney disorders. Drug Safety. 2001;24(1): 19-38.

20. 20.Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. Hematology/oncology clinics of North America. 2000; 14(1): 193-212.

21. 21.Oken M M, Creech R H, Tormey DC.et.al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6): 649-656.

BJMP 2013;6(4):a634

Review Article

Electroconvulsive Therapy (ECT): Important parameters which influence its effectiveness

Aadil Jan Shah, Ovais Wadoo, Javed Latoo

Abstract

Electroconvulsive therapy (ECT) is usually given to people with severe depression which has not responded to other forms of treatment such as anti-depressants. However, it is sometimes used for people with a diagnosis of bi-polar disorder or schizophrenia. It was originally developed in the 1930s and was used widely during the 1950s and 1960s for a variety of conditions. ECT consists of passing an electrical current through the brain to produce an epileptic fit – hence the name, electro-convulsive. The idea developed from the observation that, in the days before there was any kind of effective medication, some people with depression or schizophrenia, and who also had epilepsy, seemed to feel better after having a fit.

The mechanism of action of ECT is not fully known. ECT affects multiple central nervous system components, including hormones, neuropeptides, neurotropic factors, and neurotransmitters. The induction of a bilateral generalized seizure is required for both the beneficial and adverse effects of ECT. Certain parameters like seizure duration, electric stimuli, seizure threshold, ECT practice factors and medication can influence its efficacy or effectiveness. This study aims to review the evidence base of these parameters in detail.

Keywords: A review of literature regarding ECT was using search engines like MEDLINE, PsycInfo, and OVID using the key words "electroconvulsive therapy," "seizure parameters," "seizure duration," "seizure threshold," "stimulus dosing" and "effectiveness."

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for some individuals with severe neuropsychiatric illness. It is widely used to treat certain psychiatric disorders, particularly major depression.[1,2] ECT involves applying a brief electrical pulse to the scalp after the patients are administered muscle relaxants and general anaesthesia.[3] This pulse excites the brain cells causing them to fire in unison and produce a seizure.

In 2003, the National Institute of Clinical Excellence (NICE) issued guidance on the use of ECT. Its use was recommended only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening in individuals with severe depressive illness, catatonia or a prolonged manic episode.[4]

The mechanism of action of ECT is not fully known. ECT affects multiple central nervous system components, including hormones, neuropeptides, neurotropic factors, and neurotransmitters. The induction of a bilateral generalized seizure is required for both the beneficial and adverse effects of ECT. Certain parameters like seizure duration, electric stimuli, seizure threshold, ECT practice factors and medication can influence its effectiveness. The degree to which electrical stimulation exceeds the seizure threshold, the positioning of electrodes on the head, pulse width, pulse frequency and seizure duration are all known to be important.[5] This study aims to review the evidence base of these parameters in detail. The seizure duration and electric stimulus are the two critical parameters and are therefore the main focus of this review.

Literature Review

A review of literature regarding ECT was using search engines like MEDLINE, PsycInfo, and OVID using the key words "electroconvulsive therapy," "seizure parameters," "seizure duration," "seizure threshold," "stimulus dosing" and "effectiveness."

Parameters Associated with Effectiveness of ECT

- Seizure Duration
- Electrical Stimulus
- Seizure Threshold
- ECT Practice Factors
- Endocrine Factors
- Medication
- Other Parameters

Relationship between Seizure Duration and Effectiveness of ECT

Very little is documented on clinical studies that correlate ECT effectiveness and seizure duration. There is evidence that supports the direct relationship of seizure duration and the effectiveness of ECT. It was thought that measuring the seizure duration and the knowledge of measuring such parameters can help explain its therapeutic effect.[6] There has been research which suggests that motor seizures of less than 15 seconds in

duration do not exhibit tonic-clonic phases and are ineffective in treatment.[7] Some of the studies in past years found a direct relationship between total seizure duration during a course of treatment and patient response to ECT.[8]

A retrospective study on ward patients found that a positive clinical outcome from depressive symptoms has a direct relationship with accumulative seizure time in the course of therapy.[8] However, the study was neither randomized nor controlled. Stimulus intensity, diagnosis, and concurrent medication parameters were not properly considered. Another study that supports the correlation found that 88% of patients with cumulative seizure time of 300 seconds and over had a favourable response. The data was retrospectively and prospectively collected in a university hospital. It was mentioned that data gathering was very difficult specifically with regard to the variable number of patients' ECT sessions; the confounding effect of medication and the treatment of different patients using unilateral or bilateral.[9]

However other studies challenge these statements. A prospective study of a sample of depressed patients undergoing ECT, the seizure duration did not correlate with Hamilton Depression Rating Scale (HAM-D) scores after treatment. However, it was found that significant nonverbal memory loss of patients was correlated with seizure duration.[10] The seizure duration does not directly influence the frequency of ECT, longer seizures do not equate to fewer ECT treatments. Studies using HAM-D scores do not support the idea that seizure duration is a variable correlated to efficacy.[11] Short seizures during ECT for few patients are the result of a medical condition or drug treatment interference. On the other hand, patients who have been subjected to ECT treatment encounter shortened seizures.[12]

There are studies which show that the length of the cerebral seizure activity or the tonic–clonic convulsion is not related to clinical effectiveness.[6,13] However, the treating psychiatrist should question whether, or not, generalised cerebral seizure activity had occurred if, at the first treatment, the convulsion lasted less than 15 seconds or the EEG recording showed seizure activity lasting less than 25 seconds.[14] Such brief seizure activity might be the result of a focal or partial seizure, and therefore be of questionable therapeutic efficacy. It has been noted that there are patients who recover with ECT and yet display only short tonic–clonic convulsions. This may be more likely in elderly patients.

Most recent evidence mentions that the quality of cerebral seizure activity and the quality of the desired activity cannot simply be related to its length in time alone. It is recommended that the convulsion be timed from the end of electrical stimulation to the end of generalised, that is, bilateral, clonic activity. EEG monitoring can also be done but one needs to have good experience using this technique and sometimes artefacts can cause misinterpretation of the results.[15]

Relationship between Electric Stimulus and Effectiveness of ECT

ECT is administered by a constant-current, brief-pulse ECT machine that is able to deliver a wide range of electrical dose, that is, 25–50 mC up to 750–800 mC. It is recommended that new machines deliver a range of dose from 25 to 1000 mC.[15] One of the important parameters in predicting clinical response is the degree to which the electrical stimulus exceeds the seizure threshold.[16] The maintenance of adequate seizure duration on patients is a complicated issue. Elderly patients are also more susceptible to cognitive side effects than younger patients.[17] Patients regularly treated with ECT have records of shorten seizure duration over time, and clinicians need to increase stimulus to maintain duration, which in the long run can lead to complications.[18]

Electroencephalography (EEG) Findings

Voltage Suppression Studies. Postical voltage suppression refers to the decrease in resting EEG voltage after seizure activity as compared with baseline. Proper excitation of seizures invoke voltage-suppressing neural mechanisms intended to terminate and further seizure activity. This suppression is considered as a lower baseline on the EEG post ictus.[19]According to studies, the degree of suppression correlates with seizure generalization, therapeutic adequacy, and bilateral stimulation.[20]

EEG Waveform Features. Greater ictal EEG amplitude, intensity, and symmetry obtained with bilateral ECT are not common with longer seizures, but they are related to antidepressant outcome.[21] Studies found that the immediate post stimulus and mid ictal EEG amplitudes correlated with seizure therapeutic adequacy in depression. The symmetry of waveforms at the midpoint on the EEG tracing was also predictive.[20] It was also proven that seizure duration had no impact as an EEG measure of treatment adequacy.[21]

Seizure Charge. The calculated product of EEG voltage, seizure uniformity throughout the brain, and seizure duration was hypothesized to be a measure of treatment intensity and efficacy.[21] The variables included in total seizure charge are not physiologically independent of one another, which means longer seizure duration will not guarantee better results.

Low-dose bilateralelectroconvulsive therapy has a powerful antidepressant effectbut low-dose right unilateral therapy is ineffective.[22] Evidence shows that the efficacy of rightunilateral electroconvulsive therapy depends on the electricaldose.[23,24] There is some research showing that forboth unilateral and bilateral ECT, a higherelectrical dose leads to a more rapid clinical response.[7,17,23]

Seizure Threshold and Electroconvulsive Therapy

The knowledge of the seizure threshold is a guide to the selection of the electrical stimulus dose for ECT. In theory, the

seizure threshold is the lowest dose of electrical charge for each particular patient that is required to induce seizure.[25] In clinical applications the seizure threshold depends on individual patient's characteristics, treatment history, and other stimulus factors.[26]

The therapeutic effectiveness of ECT is partly dependent on the degree that the stimulus intensity exceeds the seizure threshold.[27,28] This statement is true on unilateral non-dominant electrode placement (UL) and on relative stimulus intensity. On bilateral (BL) ECT, the therapeutic response frequency is dependent on higher relative stimulus intensity,[28]whereas barely suprathreshold UL ECT has significantly reduced antidepressant potency in contrast to moderately suprathreshold UL ECT (150% above threshold).[6] The clinical use of this can be applied after determining the seizure threshold at the first treatment.[22,29] The desired relative stimulus intensity to be maintained during treatments is confounded by variable increase in seizure thresholds during treatment.[28] This rise in the seizure threshold lessens the degree to which a fixed stimulus dosage exceeds the seizure threshold which can result in possible diminished treatment therapeutic potency.

The seizure threshold can be higher in the elderly population and this may increase the difficulty of eliciting effective seizures.[29,30,31] The choice of anaesthetic agent and other age related factors can also affect the seizure threshold. Propofol can reduce the seizure duration and has a possible effect on the seizure threshold.[32] The seizure threshold may sometimes rise during the course of therapy. The dose would usually rise *pari passu* with a rise in the seizure threshold to maintain the dosing strategy. The seizure threshold can increase about 80% in bilateral ECT and 40% in unilateral ECT over a course of treatment.[6] Some studies found increases of only 25–40% for bilateral ECT.[33]

ECT Practice Factors and Seizure Duration

As discussed earlier, the success of ECT treatment can be related to the degree to which the electrical stimulus exceeds seizure threshold and not the absolute dose that determines clinical outcome, especially in unilateral patients.[6]Right unilateral (RUL) treatment at variable dosage can produce seizures of equal duration to bilateral treatment. With low levels electrical stimulation, RUL patients showed only 17% improvement inHAM-D scores compared to 70% in the BL group, despite the same mean seizure duration.[22]

Positioning electrodes over the non-dominant hemisphere causes lesssevere cognitive side effects than bilateral placement.[11,24] In spite of extensive research however, the relative efficacy of right unilateraland bilateral electroconvulsive therapy is controversial.[2,34,35] There are studies which have found superior efficacy with bilateral therapy,[22,36,37] and then there are other studies which have reported equivalent efficacy.[38,39] Because ofthis uncertainty, the American Psychiatric Association TaskForce on Electroconvulsive Therapy recommended thatelectrode placement be determined on a case-by-case basis.[2]

Multiple ECT stimuli (MECT) is given to patients to achieve longer cumulative seizure durations. The clinical improvement in depression correlates to patients' total seizure time in MECT. But there is no proven study on the benefits of increased seizure time from the increased number of stimuli administered.[40]

Endocrine Measures

Oxytocin. According to studies, the measurement of oxytocin released from posteriorpituitary has a direct relationship with HAM-D measured improvement in depression.[41] The concentration of oxytocin-associated neurophysin (AON) serum was calculated before and after the patient's treatment of ECT. The increase in AON positively affects HAM-D. This neurophysin response was evident on ECT treatment but does not relate to EEG-measured seizure duration.

Prolactin. The surge of prolactin released during ECT treatment can be an indicator of clinical improvement. Seizure duration is associated with a rise in prolactin.[42] However, the relationship between the magnitude of prolactin release and benefits of ECT is yet to be established.[24]

Cortisol. Although several variables have been studied as a possible predictor for the efficacy of ECT but results regarding hypercortisolism have been inconsistent. There has been a study to evaluate the relation between pre-treatment cortisol levels and the efficacy of ECT in a population of drug-free inpatients with severe major depression. This study suggests that higher levels of post-dexamethasone salivary cortisol at 9 AM are predictive of ECT efficacy.[43]

Elevated glucocorticoids may increase the vulnerability of the brain to the adverse effects of repeated seizures.This hypothesis was tested in a study and it was found that, ECT treatments delivered over 2 weeks resulted in a significant improvement in mood and a decline in most measures of cognitive performance. Elevated basal cortisol was associated with a greater decline in performance of executive function, visuospatial processing speed, and verbal memory. It was concluded that elevated cortisol predicts a greater degree of ECT-induced cognitive impairment. [44]

Medication

Concurrent medication. Concurrent therapy can be considered under two headings: general medication and psychotropic medication. Both can affect seizure threshold. Anticonvulsants, hypnotics and membrane stabilisers tend to raise the seizure threshold, while preparations containing theophyllines can have the opposite effect. Concurrent psychotropic medication can have a significant effect upon ECT. Benzodiazepines are

anticonvulsant and should be avoided if possible, but it is important to remember that there are risks associated with their sudden withdrawal. Some authorities have suggested short-term reversal with flumazenil if their presence is considered to be a limiting factor in the success of ECT, but experience is limited.[45,46] Tricyclics tend to be proconvulsant, but there is little evidence of any detrimental effect on ECT. Selective serotonin reuptake inhibitors (SSRIs) tend to reduce seizure threshold and may be associated with prolonged seizures. Monoamine oxidase inhibitors increase seizure threshold and it is essential that the anaesthetist is aware that the patient is taking this class of medication or has done so within the previous 2 weeks. Lithium reduces seizure threshold and serum levels should be checked regularly and kept within a moderate range (0.4–1 mmol/l). Selective inhibitors of the reuptake of noradrenaline in common with SSRIs, can reduce seizure threshold and also cause hypertension. Neuroleptics tend to be proconvulsant at low dosage but increase seizure thresholds at higher dosage.

In a retrospective study of 455 patients involving 5482 treatments differences in tolerability and clinical effectiveness were found between combination therapy (ECT administered together with neuroleptic medication) and ECT monotherapy.[47] Seizure duration which was assessed by EEG was significantly longer in patients treated with combination therapy using neuroleptics with lower antipsychotic potency; whereas seizure duration assessed by EEG-monitoring-electromyograph (EMG) was shorter in combination treatments done with atypical substances. In a parallel study, of ECT monotherapy or combination therapy with antidepressants using the same patient group, seizure duration was unaffected by most antidepressants but SSRIs lengthened seizure activity.[48] In addition this study found that therapeutic effectiveness was significantly enhanced in the patients receiving tricyclic antidepressants, the tetracyclic antidepressant mirtazapine or SSRIs.

There may also be a role for antidepressants in the prevention of relapse following ECT. A small double-blind placebo controlled study of the tricyclic antidepressant imipramine involving 27 depressive inpatients who had failed on pharmacotherapy prior to ECT showed that imipramine, when compared to placebo, resulted in a significant decrease in the risk of relapse of patients receiving ECT.[49] This study is in broad agreement with an earlier randomized, double-blind, placebo-controlled trial using another tricyclic antidepressant nortriptyline, or combination therapy of nortriptyline with lithium in the prevention of post-ECT relapse in patients with unipolar major depression.[50] In 29 patients receiving placebo the relapse rate during the 24 week duration of the trial was 86%; whilst in 27 patients receiving nortriptyline 60% relapsed; and 39% of the 28 patients receiving nortriptyline and lithium combination therapy relapsed during the time of the study.

Other parameters

The effectiveness of the treatment is influenced by many other underlying factors, specifically the conditions and factors relating to individual patients. This would include age, sex, physical health status, co morbidities etc. Thus, one should always consider other factors that might affect the efficacy of ECT. Two recent small Japanese studies have suggested that some cardiovascular and EEG parameters may act as markers to predict the therapeutic response of ECT in depression. Posticta l systolic heart rate and blood pressure were found to be significant predictors of the therapeutic efficacy of ECT in a study of 24 patients with depression;[51] with higher systolic heart rate and blood pressure being associated with more effective ECT.

Discussion

ECT is widely used to treat certain psychiatricdisorders, particularly major depression. Although ECT has been extensively used there is little published information on the effect of seizure parameters and the effectiveness of ECT. There is evidence that supports the direct relationship of seizure duration and the effectiveness of ECT but the latest research suggests that the length in time of the cerebral seizure activity or the tonic–clonic convulsion is not related to clinical effectiveness.[10,11] The effectiveness of ECT is related to the quality of cerebral seizure activity and cannot simply be related to its length in time alone. One of the important parameters in predicting clinical response is the degree to which electrical stimulus exceeds the seizure threshold.

Past research has shown that a generalized seizureof adequate duration is necessary and sufficient for antidepressanteffectsand that the intensity of the electrical stimuluscontributes to decreased cognitive function, the principal sideeffect, but not to effectiveness.[7] Different types of anaesthetics, or concurrent medications can affect the seizure parameters and its efficacy.[52,53] Research shows that a generalized seizureof adequate duration is necessary and sufficient for antidepressanteffects[1,7] and that the seizures of less than 15 seconds duration are ineffective. There are other studies which mention that seizure duration does not influence the effectiveness of the ECT.[10,11]

The Future

Clinicians need to continue to research this difficult area within psychiatry to enhance the evidence base and fill such gaps in this evidence as highlighted by the ECT Handbook.[54] On-going research is needed into what is a proven treatment of depressive illness and this should include more in depth research into the relationship of the above discussed parameters with its effectiveness.

"If ECT is ever legislated against or falls into disuse, it will not be because it is an ineffective or dangerous treatment, it will be

because of a failure to supervise and monitor it correctly"[55] and such supervision includes future quality research by concerned clinicians. Current NICE guidelines have limited the use of ECT to individuals with severe depressive illness, catatonia or a prolonged or severe manic episode who have been unresponsive to other treatment options.In addition, intervention of ECT should be considered to be short term and NICE does not recommend using it as maintenance therapy.[56] As research into ECT develops, the consequences may be an even more targeted approach to the use of ECT as therapy.

Acknowledgements
None
Competing Interests
None declared
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REFERENCES

1. Electroconvulsive therapy. JAMA (1985), 254, 2103-2108.
2. American Psychiatric Association (1990).The practice of electroconvulsive therapy: recommendations for treatment, training and privileging. Washington, D.C.
3. Skapanalis, P., Gerasi, E. (2008). ECT (Electro-Convulsive Therapy) Retrieved April 4, 2010 from http://web4health.info/en/answers/bipolar-treat-ect.htm
4. National Institute of Clinical Excellence (NICE) (2003). Electroconvulsive therapy (ECT). Retrieved on 2007-12-29
5. Spellman T, Peterchev AV, Lisanby SH. (2009). Focal electrically administered seizure therapy: a novel form of ECT illustrates the roles of current directionality, polarity, and electrode configuration in seizure induction. Neuropsychopharmacology. 34, 2002-2010.
6. Sackeim, H.A., Devanand, D.P., Prudic, J. (1991). Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electro convulsive therapy. Psychiatric Clinics of North America, 14, 803-843.
7. Ottosson, J.O. (1960). Experimental studies of the mode of action of electro convulsive therapy. Acta Psychiatrica Scandinavica, 145-732 - 736.
8. Maletzky, B.M. (1978). Seizure duration and clinical effect in electro convulsive therapy. Comprehensive Psychiatry, 19, 541-550.
9. Zorumski, C.F., Burke, W.J., Rutherford, J.L., Reich, T. (1986). ECT:clinical variables, seizure duration and outcome, 2,109-119
10. Miller, A.L., Faber, R.A., Hatch, J.P., Alexander, H.E. (1985). Factors affecting amnesia, seizure duration, efficacy in ECT. American Journal of Psychiatry , 142, 692-696.
11. Weiner, R.D., Coffey, D.E. (1986). Minimizing therapeutic differences between bilateral and unilateral nondominant ECT. Convulsive Therapy , 2, 261-265.
12. Fink, M. (1991).What is an adequate treatment in convulsive therapy, Acta Psychiatrica Scandinavica, 84, 224-227.
13. Weiner, R. D., Coffey, C. E., Krystal, A. D. (1991). The monitoring and management of electrically induced seizures. Psychiatric Clinics of North America, 14, 845–870.
14. Scott, A.I.F., Lock, T. (1995).Monitoring seizure activity. In The ECT Handbook (1stedn) (ed. C. P. Freeman). pp 62–66. London: Royal College of Psychiatrists.
15. Scott, A.I.F. (2005). ed. The ECT handbook. 2nd ed. London, England: Royal College of Psychiatrists
16. Fink, M. (1979). Convulsive therapy: theory and practice, New York: Raven Press
17. Robin, A., de Tissera ,S. (1982). A double-blind controlled comparison of the therapeutic effects of low and high energy electro convulsive therapies, 141,357-366.
18. Green, A.R. et al., (1982). Increased seizure threshold following convulsion. Psychopharmacology of anti-convulsants. Oxford University.
19. Mucherjee, S. (1989). Mechanism of the antimanic effect of electro convulsive therapy. 5, 337-343.
20. Krystal, A.D., Weiner ,R.D. (1994). ECT seizure therapeutic adequacy. Convulsive Therapy, 19, 153-164.
21. Nobler, M.S., Sackeim, H.A., Solomou, M., Luber, B., Devanand, D.P., Prudic, J. (1993). EEG manifestations during ECT: effect of electrode placement and stimulus intensity. Biological Psychiatry 34, 321-330.
22. Sackeim, H.A., Decina, P., Kanzler, M., Kerr, B., Malitz, S. (1987). Effects of electrode placement on the efficacy of titrated, low-dose ECT. Am J Psychiatry 144,1449-1455.
23. Abrams, R. (1986). Is unilateral electroconvulsive therapy really the treatment of choice in endogenous depression? Ann N Y Acad Sci ,462,50-55.
24. Sackeim ,H.A., Mukherjee, S. (1986). Neurophysiological vareiability in the effects of the the ECVT stimulus, Convulsive Therapy, 2, 267-276.
25. Janakiramaiah, N., Rao, K.M., Praveen, J., Sujatha, B.L., Gangadhar, B.N., Subbakrishna, D.K. (1992). Seizure duration over ect sessions: influence of spacing ects, Indian Journal of Psychiatry, 34,124-127.
26. Weiner, R.D (1980). ECT and seizure threshold: Effects of stimulus waveform and electrode placement, Biological Psychiatry, 15, 225-241.
27. Sackeim, H.A, Prudic, J. Devanand, D.P. Kiersky, J.E. Fitzsimons, L., Moody B.J., et al., (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med, 328(12), 839-846.
28. Krystal, A.D. Weiner, R.D. Coffey, C.E. (1995). The ictal EEG as a marker of adequate stimulus intensity with unilateral ECT. J Neuropsychiatry Clin Neurosci 7, 295-303.
29. Coffey, C.E, Lucke ,J.Weiner ,R.D. Krystal, A.D. Aque, M. (1995). Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. Biol Psychiatry , 37,(11) 777-788.
30. Sackeim, H.A., Decina, P., Prohovnik, I., Malitz, S. (1987). Seizure threshold in electroconvulsive therapy: effects of sex, age, electrode placement, and number of treatments. Arch Gen Psychiatry 454, 355-360.
31. Boylan, L.S, Haskett, R.F, Mulsant, B.H, Greenberg, R.M, Prudic, J. Spicknall,K. et al., (2000). Determinants of seizure threshold in ECT: benzodiazepine use, anesthetic dosage, and other factors. J ECT 16, 3–18.
32. Alexopoulos, O.S, Shamoian, C.J, Lucas, J. Welser, N & Berger,H. (1984). Medical problems of geriatric psychiatric patients and younger controls during electroconvulsive therapy. Journal of the American Geriatrics Society, 32, 651- 654
33. Scott, A.I.F., Boddy, H. (2000). The effect of repeated bilateral ECT on the seizure threshold. Journal of ECT, 16, 244-251.
34. Abrams, R. (1986). A hypothesis to explain divergent findings among studies comparing the efficacy of unilateral and bilateral ECT in depression. Convulsive Therapy, 2, 253-257.

35. Ottosson, J.O. (1991). Is unilateral nondominant ECT as efficient as bilateral ECT? A new look at the evidence. Convulsive Therapy, 7, 190-200.
36. Abrams, R. Taylor, M.A. Faber, R. Ts'o, TO. Williams, R.A. Almy, G. (1983). Bilateral versus unilateral electroconvulsive therapy: efficacy in melancholia. Am J Psychiatry, 140, 463-465.
37. Gregory, S., Shawcross, C.R, Gill, D. (1985). The Nottingham ECT Study. A double-blind comparison of bilateral, unilateral and simulated ECT in depressive illness. Br J Psychiatry. 146, 520-524.
38. Weeks, D. Freeman, C.P. Kendell, R.E. (1980). ECT: III: Enduring cognitive deficits? Br J Psychiatry 137, 26-37.
39. Horne, R.L. Pettinati ,H.M. Sugerman, A.A. Varga, E. (1985). Comparing bilateral to unilateral electroconvulsive therapy in a randomized study with EEG monitoring. Arch Gen Psychiatry, 42, 1087-1092.
40. Abrams, R., Volavka, J., Fink, M. (1973). EEG seizure patterns during multiple unilateral and bilateral ECT, Comprehensive Psychiatry, 14, 25-28.
41. Scott, A.I., Whalley, L.J., Legros, J.J. (1989). Treatment outcome, seizure duration, and the neurophysin response to ECT, Biological Psychiatry. 25, 585-597.
42. Abrams, R & Swartz, C.M. (1985). Electro convulsive therapy and prolactin release: effects of stimulus parameters. Convulsive Therapy, 1, 38-42.
43. Neylan,T.C.,Canick, J D., Hall, S.E et,al., (2001). Cortisol Levels predict cognitive impairment induced by ECT. Biological Psychiatry, 1:50 (5):331-6.
44. Vukadin,M., Birkenhäger,T.K., Wierdsma, A.I., et,al., (2011). Post-dexamethasone cortisol as a predictor for the efficacy of electroconvulsive therapy in depressed inpatients. Journal of Psychiatric Research, 45(9):1165-9.
45. Bailine, S.H., Safferman, A., Vital-Herne, J., Bernstein, S. (1994). Flumazenil reversal of benzodiazepine-induced sedation for a patient with severe pre-ECT anxiety. Convulsive Therapy, 10, 65–68.
46. Hanania, M. M. (1995). Flumazenil reversal of benzodiazepine sedation before electroconvulsive therapy. Anesthesiology, 82, 321.
47. Nothdurfter, C, Eser, D, Schüle, C, Zwanzger, P, Marcuse, A, Noack I, et al. (2006). The influence of concomitant neuroleptic medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. World J Biol Psychiatry. 7(3), 162-170.
48. Baghai, TC, Marcuse, A, Brosch, M, Schüle, C, Eser, D, Nothdurfter, C et al. (2006). The influence of concomitant antidepressant medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. World J Biol Psychiatry. 7(2), 82-90.
49. van den Broek, W.W., Birkenhäger, T.K., Mulderm P.G., Bruijnm J.A., Moleman, P. (2006). Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. J Clin Psychiatry. 67, 263-268.
50. Sackeim H.A., Haskett R.F., Mulsant B.H., Thase M.E., Mann J.J., Pettinati H.M. et al. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA. 285(10), 1299-1307.
51. Azuma, H, Fujita, A, Sato, K, Arahata, K, Otsuki, K, Hori, M, et al. (2007a). Postictal cardiovascular response predicts therapeutic efficacy of electroconvulsive therapy for depression. Psychiatry Clin Neurosci. 61(3), 290-294.
52. Eser, D, Nothdurfter, C, Schüle, C, Damm, J, Steng, Y, Möller, HJ, et al. (2010). The influence of anaesthetic medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. World J Biol Psychiatry. 11(2 Pt 2), 447-456.
53. Dinwiddie, S.H., Glick, D.B., Goldman, M.B. (2011). The effect of propofol-remifentanil anesthesia on selected seizure quality indices in electroconvulsive therapy. Brain Stimul. Jul 26 2011. [Epub ahead of print].
54. Royal College of Psychiatrists (2005). ECT Handbook: The Third Report of the Royal College of Psychiatrists' Special Committee on ECT, 2nd Edition. ed. I.A.F. Scott . The Royal College of Psychiatrists.
55. Lancet (1981) (ed) ECT in Britain: A shameful state of affairs. Lancet 318, (8257), 1207-1208.
56. National Institute for Health and Clinical Excellence (NICE) (2010). Electroconvulsive therapy (ECT). Available from http://www.nice.org.uk/TA059. Accessed 27th September 2011.

Review Article

BJMP 2013;6(4):a629

Biologics in Dermatology: A Brief Review

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Abstract
With the advent of biologic therapy, the treatment of various systemic and cutaneous diseases, especially autoimmune diseases, has been revolutionized. Most of the treatment modalities available prior to biologics aimed at producing clinical improvement of the disease without targeting the actual causative factors. Biologics are protein molecules produced by recombinant DNA technology, which target the specific sites in the immune-pathogenesis pathway of the diseases. Because of the specific action on immune system, biologics are presumed to have lesser side effect profile compared to the traditional immune-suppressants. However, the use of biologics is still limited because of unknown long-term safety profile and various aspects of the biologics need to be thoroughly evaluated by conducting large scale studies worldwide. In this review we give a brief description of various biologic agents that are known till date.
Keywords: Biologics; proteins; autoimmune diseases.

INTRODUCTION

The US Food and Drug Administration (USFDA) considers the following as biologics: any therapeutic serum, toxin, antitoxin, vaccine, virus, blood, blood component or derivative, allergenic product, analogous product, or derivatives applicable to the prevention, treatment, or cure of injuries or disease of man[1]. However, generally, biologics refer to protein molecules therapeutically used in various diseases so as to target specific points in the inflammatory cascade of these disorders [2]. Hope for an improved tolerability, convenience in usage and lasting remissions, combined with increased knowledge of immune-pathogenesis of various cutaneous diseases has led to the introduction of biologics as alternative immune-modulating agents in the field of dermatology.

CLASSIFICATION

Biologics are generally divided into three major groups [3]:

a) Monoclonal antibodies
b) Fusion antibody proteins
c) Recombinant human cytokines and growth factors

The main groups and the principal agents in each group are summarised in Box 1 and described below.

A) MONOCLONAL ANTIBODIES

Monoclonal antibodies target specific cell-surface receptors. In the early days of biologic therapy, purely murine monoclonal antibodies were used. However, due to the development of antimurine antibodies, which blocked their action, these could be given only for very short periods. The monoclonal antibodies used now have different amounts of murine sequences in the variable region. They may be categorised into three classes:

(a) chimeric antibodies comprising of 30% murine genes fused with human antibodies
(b) humanised antibodies, which have 10% murine sequences, and
(c) human antibodies, which are solely derived from human immunoglobulin genes 4.

Principal monoclonal antibodies with therapeutic relevance in Dermatology

The principal monoclonal antibodies known till date are enumerated in Box 1 and described briefly below.

1. Infliximab

Infliximab (trade name Remicade) is a human-mouse monoclonal antibody that binds to and inhibits the activity of TNF-α, and also causes lysis of TNF-α producing cells[5].

Important uses of Infliximab

Psoriasis: Infliximab is approved for the treatment of psoriatic arthritis and plaque psoriasis by FDA[6, 7]. Infliximab may also be of value in recalcitrant or unstable disease and in generalised pustular psoriasis. It is given as an IV (intravenous) infusion in doses of 5 or 10 mg/kg, over a period of 2 hours at weeks 0, 2, 6 and may be followed by repeat single infusions at 8-12 week intervals [8]. In various controlled trials, improvement at 10 weeks has been noted in 87% of patients [7, 9].

Atopic dermatitis: Infliximab has also been evaluated in a study of atopic dermatitis [10]. At 2 weeks, there was significant

improvement in all patients. At 10, 14, and 30 weeks, variable response was seen.

Box 1: Classification of biologics

Monoclonal antibodies

- Anti-TNFα: Infliximab, Adalimumab, Certolizumab, Golimumab
- Anti-LFA1: Efalizumab
- Anti-CD20: Rituximab
- Anti-IL-12 and anti-IL-23 monoclonal antibody: Ustekinumab
- Anti-CD2 antibody: Siplizumab
- Anti-CD4 antibody: Orthoclone (OKTcdr4a)
- Anti-CD25 antibodies: Basiliximab, Daclizumab
- Anti-CD80r: Galiximab (IDEC 114)
- Anti-IgE: Omalizumab

Fusion antibody proteins

- Etanercept
- Alefacept
- Abatacept
- Onercept
- Denileukin Diftitox

Recombinant human cytokines and growth factors

a) Interferons

- Interferon α (IFNα)
- Interferon γ (IFNγ)
- Interleukin 1 Receptor antagonist (IL1Ra)
- Interleukin 2 (IL-2)
- Interleukin 4 (rhIL-4)
- Interleukin 10 (rhIL-10)
- Interleukin 11 (rhIL-11)

b) Granulocyte macrophage colony stimulating factor (GM-CSF)

c) Platelet derived growth factor (PDGF)

Hidradenitis suppurativa: Long-term efficacy has also been evaluated in hidradenitis suppurativa. In one study, some patients had no evidence of recurrence after 2 years, while others relapsed within a mean of 8.5 months[11].

2. Adalimumab

Adalimumab (Humira®) is a human IgG1 monoclonal antibody directed against TNF-α. Adalimumab is given in a dose of 40 mg subcutaneously (SC) every other week as self-injection [5, 12].

Important uses of Adalimumab

Psoriasis: Adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques [13]. In a trial, patients with psoriatic arthritis received adalimumab every other week for 24 week[14]. It was well-tolerated and helped improve joint and skin manifestations significantly.

Hidradenitis suppurativa: An increasing number of reports in refractory hidradenitis supprativa have shown successful control with adalimumab [15, 16, 17].

3. Basiliximab

Successful treatment for severe psoriasis and generalised pustular psoriasis has been reported with basiliximab, an interleukin-2 receptor (IL-2R; CD25) chimeric monoclonal antibody [18, 19].

4. Daclizumab

Daclizumab is a humanised monoclonal antibody thatbinds to the CD25 subunit of the IL-2 receptor onT-cells, thus blocking T-cell proliferation. It has been tried in recalcitrant psoriasis and HIV-associated psoriatic erythroderma with a mean reduction in PASI of 30% [20, 21 22].

5. Siplizumab

Siplizumab (Medi-507) is a humanisedmonoclonal antibody directed against CD2. It is designed to block stimulationby inhibiting the CD2–LFA-3 interaction. In earlyphase studies in psoriasis, significant response to therapy has been noted[23].

6. Efalizumab

Efalizumab is a recombinant humanised monoclonal IgG1 antibody that binds to CD11a, a subunit of leukocyte function-associated antigen 1 (LFA-1) [24]. It destabilises and decreases the trafficking of T-cells into dermal and epidermal tissues.

Important uses of Efalizumab

Psoriasis: Efalizumab was approved by the US FDA in October 2003 for the treatment of psoriasis[5]. It is currently the only biologic agent approved for continuous administration to adult patients[24]. The licensed dose of efalizumab is 1 mg/kg weekly as a subcutaneous self- administered injection for 12 weeks, following a first conditioning dose of 0.7 mg/kg [24].

Lichen planus: There is one case report of 3 months duration of treatment with efalizumab for lichen planus with resolution of skin lesions and pruritis [25].

7. Rituximab

Rituximab is a monoclonal humanised antibody directed again in the B cell-specific antigen CD20.

Important uses of Rituximab

Lymphoma: It has been used in patients with CD20-positive

non-Hodgkin's lymphoma in a dosage of 375 mg/m^2 for four infusions[26].

SLE: In systemic lupus, dose escalation studies revealed no differences with respect to clinical outcome in patients who received either a single infusion of 100 mg/m^2, a single infusion of 375 mg/m^2, or four weekly infusions of 375 mg/m^2[27].

Blistering diseases: For patients with blistering diseases, most patients receive the lymphoma dosage schedule. However, serious side effects were considerably higher.

There are reports of refractory pemphigus patients who received infusions of rituximab and had rapid resolution of lesions and a long lasting clinical remission [28, 29, 30].

8. Galiximab

Galiximab a humanised monoclonal antibody directedagainst CD80 and blocks its interaction with CD28 on the T cell, for T-cell stimulation [31]. Clinicaldata for this drug are just beginning to emerge with 40% of patients achieving at least 50% reduction in PASI after receiving4 biweekly doses in a trial[32, 33].

9. Ustekinumab

It is a fully human monoclonal antibody targeting IL-12 and IL-23, presently undergoing clinical trials for psoriasis and psoriatic arthropathy[2, 34]. In placebo-controlled studies, (PHOENIX 1) and (PHOENIX 2) have shown that ustekinumab could control plaque psoriasis with only four injections a year resulting in greater ease of use and more sustained relief[35, 36].

10. Certolizumab pegol

Certolizumab is the recombinant antibody Fab' fragment of a humanised TNF inhibitor monoclonal antibody. A study in chronic plaque psoriasis showed that certolizumab pegol, given subcutaneously every two weeks, over a period of 12 weeks shows significant improvement [37].

11. Golimumab

Golimumab, a fully human monoclonal antibody is at present undergoing Phase III clinical trials in psoriatic arthropathy [38].

12. Orthoclone or OkT4a

It is a humanised antihuman CD4 IgG4 monoclonal antibody preventing the recognition of the MHC-bound antigen by an appropriate T-cell receptor, hence T cells do not get activated [39]. Several studies have found orthoclone to be effective in moderate to severe psoriasis [40, 41].

13. ABX-IL8

ABX-IL8 is a fully human monoclonalantibody designed to bind free IL-8, a key chemokine in psoriasis and deactivate it in theskin[42, 43]. In early trials, the drug has demonstrated good clinical responsein psoriasis [44, 45].

14. Omalizumab

Omalizumab is a recombinant, humanised, monoclonal antibody against immunoglobulin IgE. This agent acts as a neutralising antibody by binding IgE at the same site on IgE as its high-affinity receptor, FcεR$_1$, thus inhibiting the biological effects before the generation of allergic symptoms [46]. There are reports of the efficacy of omalizumab in chronic urticaria [47], cold urticaria [48] and atopic dermatitis [49].

15. Mepolizumab

Mepolizumab is a humanised monoclonal IgG antibody to the IL-5 molecule, which is essential for eosinophil growth and differentiation. Two weekly infusions showed significant clinical improvement in atopic dermatitisand clinical trials are underway for hyper-eosinophillic disorders [50, 51].

16. SMART Anti–IFN-γ

SMART anti–IFN- γ,a humanised monoclonal antibody, binds and inactivates IFN- γ, an important Th1 cytokinein psoriasis. Early phase studies are being performed at this time [52].

B) FUSION ANTIBODY PROTEINS

Fusion proteins, also known as chimeric proteins, are proteins which are created by the fusion of the receptor domain of a human protein with the constant region of human IgG. The resultant fusion protein binds specifically to a ligand or co-receptor [53]. The most commonly used fusion proteins in dermatology are briefly described below and enumerated in Box 1.

1. Alefacept

Alefacept is a bivalent recombinant fusion protein composed of the first extracellular domain lymphocyte function antigen 3 (LFA-3), fused to the hinge domain of human IgG1. The LFA-3 portion of alefacept binds to CD2 receptors on T-cells, thereby blocking their natural interaction with LFA-3 on antigen presenting cells (APCs). The IgG1 portion of alefacept binds to FcγR receptor on natural killer cells to induce T-cell apoptosis [54].

Important uses of Alefacept

Psoriasis: The US FDA approved alefacept in January 2003 for treatment in adult patients with moderate to severe chronic plaque psoriasis. It is given by intramuscular or intravenous route with a dose of 10-15 mg IM weekly or 7.5 mg IV weekly

and a 12 week course is recommended [5, 54]. Two 12-week courses showed a75% or greater reduction in the PASI [55].

Alopecia areata: Case reports have shown that alefacept may be effective in the treatmentof AA[56, 57].

Pyoderma gangrenosum: Alefacept has been used for pyoderma gangrenosum and improvement was shown in 25% of these patients [58].

Other Indications

Some of the off-label conditions where alefacept has been used with success are graft-versus-host disease (GVHD), lichen planus, alopecia areata, atopic dermatitis, mycosis fungoides,alopecia universalis, erosive lichen planus,Hailey-Hailey diseaseand hand dermatitis [58, 59, 60, 61, 62, 63].

2. Denileukin diftitox

Denileukin diftitox is a novel recombinant fusion protein consisting of fragments of diphtheria toxin linked to human interleukin-2 and works by targeting the high-affinity interleukin-2 receptors. It was tried in patients with recalcitrant psoriasis and the rate of improvement for treated patients was found to be significant [64].

3. Abatacept (Ctla4ig)

It is a fusion protein composed of the extracellular domain of CTLA4 and the Fc region of IgG4. It interferes with T-cell activation by competitively binding the B7.1 and B7.2 molecules on the surface of APC [65]. In a study, patients with stable psoriasis vulgaris showed good improvement with IV infusion of abatacept [33]. A second generation CTLA4Ig, Belatacept, is currently under Phase II clinical trial for allograft diseases [66].

4. Etanercept

Etanercept is a recombinant fully human dimeric fusion protein comprising of the human TNF-α p75 receptor and the Fc portion of human IgG1 molecule. It functions as a TNF inhibitor, thereby preventing interaction with its cell surface receptors on target cells and blocking its pro-inflammatory effects.

Important uses of Etanercept

Psoriasis: Etanercept (Enbrel®) is FDA approved for use as subcutaneous monotherapy in psoriasis. Several clinical trials have shown that it is effective[67, 68, 69, 70]. The adult dose is 50 mg/week, given subcutaneously for three months [5]. The drug is also indicated for treatment of psoriatic arthritis [71, 72].

Hidradenitis supprivata:There is a study of etanercept in patients with severe hidradenitis with more than 50% score improvement[12].

5. Onercept

Onercept is a recombinant human soluble p55 tumour necrosis factor binding protein under development for the potential treatment of psoriasis and psoriatic arthritis[73].

C) RECOMBINANT HUMAN CYTOKINES AND GROWTH FACTORS

Cytokines are non-immunoglobulin proteins and glycoproteins produced by a wide variety of cells in the human body and released in response to any immune stimulus [74, 75]. Recombinant cytokines or cytokine antagonists have been used as immunomodulators [76]. The principal recombinant cytokines used in dermatology, enumerated in Box 1, are described below.

1. Interferons (IFNs)

IFNs, a family of related proteins, are produced by virus-infected leucocytes. They exhibit anti-proliferative, immune-modulatory and anti-neoplastic functions [77].

· ***Interferon α***

Recombinant IFNα is given as a subcutaneous or intramuscular injection to treat verruca vulgaris [78] , condyloma acuminatum [79], cutaneous T cell lymphoma [80], Kaposi's sarcoma (AIDS related) [81], melanoma [82], basal cell carcinoma [83], squamous cell carcinoma [84], actinic keratosis [85], Behçet's disease [86], hemangiomas [87] and keloids [88].

The injections are usually given thrice weekly and the dose (depending on the condition being treated) varies from low-dose therapy for condyloma acuminatum to high-dose therapy for melanoma [89, 90]. Of late, pegylated IFNα is being used for convenience, because it has a longer half-life and hence can be given once weekly [80].

· ***Interferon-γ***

It is FDA approved for the treatment of chronic granulomatous disease [91] and has also been used in atopic dermatitis [92]and cutaneous T cell lymphoma [90].

2. Interleukin 1 receptor antagonist (IL1Ra, Anakinra)

Anakinra is the non-glycosylated form of human IL-1Ra and acts by blocking the functions of the naturally occurring IL-1[93]. Good results have also been reported in Schnitzler's syndrome[94], familial cold auto-inflammatory syndrome [95] and psoriatic arthropathy[96]. It is given by subcutaneous injection 100 mg once a day.

3. Interleukin 2

Recombinant IL-2 is an antitumour cytokine that has been used in cutaneous T cell lymphoma (CTCL) and metastatic melanoma [97]. When given intravenously in high doses of 600,000-720,000 IU/kg in melanoma, IL-2 has produced a 15-20% overall response, with complete cure in 4-6% [98].

4. Interleukin 4 (rhIL-4)

In a dose-escalation study (0.5 to 5mg/kg given by subcutaneous injection thrice a week), IL-4 has been shown to cause improvement in psoriasis by inducing Th2 differentiation in human $CD4^+$ T cells [99].

5. Interleukin 11 (rhIL-11, Oprelvekin)

It has also shown reasonably good results in the treatment of psoriasis at doses of 2.5 or 5mg/ kg, by subcutaneous injection [100].

6. Granulocyte macrophage colony stimulating factor (GM-CSF)

GM-CSF acts by stimulating stem cells to produce granulocytes, monocytes and macrophages [101]. Recombinant human GM-CSF has been used to promote wound healing in ulcerated skin for example leg ulcers [102, 103], and for the treatment of melanoma [104] and Sezary syndrome [105].

7. Platelet derived growth factor (PDGF)

PDGF is a dimeric glycoprotein which regulates and promotes granulation tissue formation, re-epithelialisation and wound angiogenesis [106]. Recombinant PDGF-BB topical gel (100ìg/g), applied once daily, has been approved by FDA for the treatment of diabetic foot ulcers [107, 108].

8. Recombinant Human IL-10

Recombinant Human IL-10 (Tenovil)can be given in subcutaneousinjections. Early phase clinical trials have shown thatrecombinant human IL-10 three times a week improved psoriasis [109, 110].

SIDE EFFECTS OF BIOLOGICS [5, 111, 112, 113]

Some of the adverse effects of biologics are described below:

- Allergic reaction and antibody formation: Mostly seen with TNF-α blockers.
- Mild transient injection site reactions: Comprising of erythema, oedema and bruising, noted with etanercept in 10-20% of cases in the first month of therapy. Antibodies to etanercept may develop in 6% of patients.
- Infusion reaction: Occurs during or within 1-2 hours of treatment and may affect up to 20% of all the patients treated with infliximab, rarely anaphylactic shock may occur.
- Acute flu-like symptoms: Headache, chills, fever, nausea and myalgia may occur within 48 hours after administration of the first two doses of efalizumab and Interferon α.
- Infections: Reactivation of tuberculosis may occur on treatment with anti-TNF-α agents and sepsis secondary to*Listeria monocytogenes* and *Histoplasma capsulatum* have been reported [113].
- Malignancy: Patients previously treated with PUVA represent an at-risk group.
- Demyelinating disease: Worsening of multiple sclerosis and demyelination reported with infliximab.
- Thrombocytopenia: Occurs with efalizumab and warrants discontinuation of therapy.
- Autoimmune haemolytic anemia: Occurs 4-6 months after the start of treatment with efalizumab.
- Congestive cardiac failure: Worsening of congestive cardiac failure with TNF-α blockers is reported to occur.
- Antinuclear antibodies and lupus-like syndrome: May develop during therapy with anti-TNF-α agents, but not associated with symptoms and signs of lupus in the majority.
- Hepatitis: Reported following infliximab therapy, occurring from 2 weeks to more than a year after initiation of treatment. Treatment should be stopped in the event of jaundice and/ or marked elevations (>5 times the upper limit of normal) in liver enzymes.

PATIENT SCREENING FOR BIOLOGIC THERAPY [113, 114]

All patients to be put on biologics should undergo a thorough evaluation including detailed clinical history, physical examination and relevant investigations with particular reference to known toxicity profile of the agent being considered. The investigations generally advised are[113]: full blood count, liver and renal function tests, screening for hepatitis and HIV infection, anti-nuclear antibodies, anti-ds DNA, urine analysis, chest X-ray and Tuberculin skin testing.

For efalizumab, haemogram (including platelet count) is recommended monthly for the first 3 months and then every 3 months. For TNF blockers, it is done at 3 months initially and repeated every 6 months.

Liver and renal function tests, serum electrolytes and urine analysis are done at 3 months initially and then every 6 months.

EXCLUSION CRITERIA/ CONTRAINDICATIONS

There are various contraindications for use of biologics, warranting their exclusion and precautions are to be exercised

because of their immune-modulator properties. The main exclusion criteria are: active tuberculosis, severe congestive heart failure, patients having >200 treatments of PUVA (because of a risk of developing malignancies with anti- TNF agents), history of demyelinating disease or optic neuritis, hepatitis B and C positivity, HIV positivity, premalignant states, active infections and high risk states such as chronic leg ulcers, persistent or recurrent chest infections and indwelling urinary catheter infections, pregnancy and breast-feeding.

ASSESSMENT OF THE RESPONSE TO BIOLOGICS

Many scoring systems for assessing the severity of various dermatological diseases exist. These scoring systems and other indices can be used for assessment of response to the use of biologics. For example, for evaluation of improvement in psoriasis, PASI (psoriasis area and severity index) and DLQI (dermatology life quality index) are recommended at 3 months initially and then every 6 months [113]. Reduction in baseline PASI score of >75% is the standard used by FDA to assess the efficacy of a new psoriasis agent [115]. Similarly in atopic eczemas, improvement is monitored based on the Eczema Area and Severity Index, Pruritus Severity Assessment and DLQI. Reduction of the Eczema Area and Severity Index score by 50% is considered excellent, 30-49% moderate and <29% non-significant.

SUMMARY

To summarise, biologics represent the future of therapeutics, not only in dermatology but also in other fields of medicine. Among the various dermatological disorders where they are used, biologics have been most evaluated in psoriasis [116]. However, the possibility of serious infections and the oncogenic potential combined with the high cost of the drugs limit their routine use at the present stage [117]. Regular re-evaluation of efficacy and safety is essential if these agents are to be used to the maximum benefit of patients[118].

Acknowledgements
Peerzada Sajad and Konchok Dorjay
Competing Interests
None declared
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REFERENCES

1. Feldmann M, Steinman L. Design of effective immunotherapy for human autoimmunity. Nature 2005; 435: 612-9.
2. Dogra A, Salonie S. Biologic therapy in psoriasis. Indian J Dermatol Venereol Leprol 2006: 72: 256-65.
3. Stern DK, Tripp JM, Ho VC, Lebwohi M. The use of systemic immune moderators in dermatology. In: Maclean DI, Maddin WS, editors. Dermatologic clinics. Vol. 23. Elsevier; 2005. p. 275.
4. Waldmann TA. Immunotherapy: Past, present and future. Nat Med 2003; 9: 269-77.
5. Kormeili T, Lowe NJ, Yamuchi PS. Psoriasis: Immunopathogenesis and evolving immunomodulators and systemic therapies; U.S experiences. Br J Dermatol 2004; 151: 3-15.
6. Antoni CE, Kruegere GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infiliximab improves signs and symtoms of psoriatic arthritis the IMPACT 2 trial.Ann Rheum Dis 2005; 64: 1150-7.
7. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al . Infliximab induction therapy for patients with severe plaque type psoriasis: A randomized, double-blind, placebo controlled trial. J Am Acad Dermatol 2004; 51: 534-42.
8. Winterfield L, Menter A. Psoriasis and its treatment with infliximab-mediated tumour necrosis factor a blockade. Dermatol Clin 2004; 22: 437-44.
9. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab montherapy for plaque type psoriasis: A randomized trial. Lancet 2001; 35: 1842-7.
10. Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol. 2005; 2: 522-6.
11. Giamarellos-Bourboulis EJ, Pelekanou E, Antonopoulou A, Petropoulou H, Baziaka F, Karagianni V, et al. An open-label phase II study of the safety and efficacy of etanercept for the therapy of hidradenitis suppurativa. Br J Dermatol 2008; 158: 567-72.
12. Scheinfeld N. Adalimumab (HUMIRA): A review. J Drugs Dermatol 2003; 2: 375-7.
13. Gordon KB, Bonish BK, Patel T, Leonardi CL, Nickloff BJ. The tumour necrosis factor-alpha inhibitor adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques. Br J Dermatol 2005; 153: 945-53.
14. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005; 52: 3279-89.
15. Blanco R, Martínez-Taboada VM, Villa I, González-Vela MC, Fernández-Llaca H, Agudo M, et al. Long-term Successful Adalimumab Therapy in Severe Hidradenitis Suppurativa. Arch Dermatol 2009; 145: 580-84.
16. Moul DK, Korman NJ. Severe hidradenitis suppurativa treated with adalimumab. Arch Dermatol 2006; 142: 1110-2.
17. Scheinfeld N. Treatment of coincident seronegative arthritis and hidradenitis suppurativa with adalimumab. J Am Acad Dermatol 2006; 55: 163-4.
18. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximа, an interleukin-2 receptor monoclonal antibody. Clin Exp Dermatol 2000; 25: 195-7.
19. Salim A, Emerson RM, Dalziel KL. Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). Br J Dermatol 2000; 143: 1121-2.
20. Wohlrab J, Fischer M, Taube KM, Marsch WC. Treatment of recalcitrant psoriasis with daclizumab. Br J Dermatol 2001; 144: 209-10.
21. Dichmann S, Mrowietz U, Schopf E, Norgauer J. Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-

associated psoriatic erythroderma. J Am Acad Dermatol 2002; 47: 635-6.
22. Krueger JG, Walters IB, Miyazawa M, Gilleaudeau P, Hakimi J, Light S, et al. Successful in vivo blockade of CD25 (high-affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. J Am Acad Dermatol 2000; 43: 448-58.
23. Langley R, Roenigk HH, McCall C, Stricklin G, Dingivan C. Phase I results of intravenous MEDI-507, an anti-T-cell monoclonal antibody, for the treatment of psoriasis. J Invest Dermatol 2001; 117: 817.
24. Leonardi CL. Current concepts and review of efalizumab in the treatment of psoriasis. Dermatol Clin 2004; 22: 427-35.
25. Bohm M, Luger T. Lichen planus responding to efalizumab. J Am Acad Dermatol 2007; 56: 92-3.
26. Leandro M, Edwards J, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. Ann Rheum Dis 2002; 61: 883-8.
27. Anolik JH, Barnard J, Cappione A, Pugh-Bernard AE, Felgar RE, Looney RJ, et al. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematous. Arthritis Rheum 2004; 50: 3580-90.
28. Ahmed A, Spiegelman Z, Cavacini L, Posner M. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006; 355: 1772-9.
29. Faurschou A, Gniadecki R. Two courses of rituximab for recalcitrant pemphigus vulgaris. Int J Dermatol 2008; 47: 292-4.
30. Schmidt E, Brockerm E, Goebeler M. Rituximab in treatment-resistant autoimmune blistering skin disorders. Clin Rev Allergy Immunol 2008; 34: 56-64.
31. Mitra RS, Judge TA, Nestle FO, Turka LA, Nickoloff BJ. Psoriatic skin-derived dendritic cell function is inhibited by exogenous IL-10: differential modulation of B7-1 (CD80) and B7-2 (CD86) expression. J Immunol 1995; 154: 2668-77.
32. Gottlieb A, Abdulghani A, Totoritis M, Lizambri R, Shuey S, Romano P, et al. Results of a single-dose, dose-escalating trial of an anti-B7 monoclonal antibody (IDEC-114) in patients with psoriasis. J Invest Dermatol 2000; 114: 840.
33. Gottlieb AB, Kang S, Linden KG, Lebwohl M, Menter A, Abdulghani AA, et al. Results of a multiple-dose, multiple schedule trial of an anti-CD80 monoclonal antibody (IDEC-114) in patients with psoriasis. Poster presented at: annual meeting of the American Academy of Dermatology; March 2, 2001; Washington, DC.
34. Krueger GG, Langley RG, Leonardi C.A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356: 580-92.
35. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX). Lancet 2008; 371: 1665-74.
36. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al . Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo- controlled trial (PHOENIX). Lancet 2008; 371: 1675-84.
37. Melmed GY, Targan SR, Yasothan U. Certolizumab pegol. Nat Rev Drug Discov 2008; 7: 641-2.
38. Hutas G. Golimumab: A fully human monoclonal antibody against TNF alpha. Curr Opin Mol Ther 2008; 10: 393-406.
39. Rao PE, Kroon DJ. Orthoclone OKT3: Chemical mechanisms and functional effects of degradation of a therapeutic monoclonal antibody. Pharm Biotechnol 1993; 5: 135-58.
40. Bachelez H, Flageul B, Dubertret L, Fraitag S, Grossman R, Brousse N, et al. Treatment of recalcitrant plaque psoriasis with a humanized non-depleting antibody to CD4. J Autoimmun 1998; 11: 53-62.
41. Gottlieb AB, Lebwohl M, Shirin S, Sherr A, Gilleaudeau P, Singer G, et al . Anti-CD4 monoclonal antibody treatment of moderate to severe psoriasis vulgaris: Results of a pilot, multicenter, multiple-dose, placebo-controlled study. J Am Acad Dermatol 2000; 43: 595-604.
42. Barker JN, Jones ML, Mitra RS, et al. Modulation of keratinocyte-derived interleukin-8 which is chemotactic for neutrophils and T lymphocytes. Am J Pathol 1991; 139: 869-76.
43. Biasi D, Carletto A, Caramaschi P, Bellavite P, Maleknia T, Scambi C, et al. Neutrophil functions and IL-8 in psoriaticarthritis and in cutaneous psoriasis. Inflammation 1998; 22: 533-43.
44. Krueger GC, Lohner M, Roskos L, Hwang CC, Bell G, Schwab G. Clinical trials results: a fully human anti-IL-8 antibody in patients with moderate to severe psoriasis. Poster presented at: annual meeting of the American Academy of Dermatology; March 2, 2001; Washington, DC.
45. Lohner M, Krueger J, Gottlieb A, Beutner K, Levy R, Wiesenhutter C, et al. Clinical trials of a fully human anti-IL-8 antibody for the treatment of psoriasis. Br J Dermatol 1999; 141: 989.
46. Mankad VS. Omalizumab: Other indications and unanswered questions. Clin Rev Allergy Immunol 2005; 29: 17-30.
47. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol 2007; 99: 190-3.
48. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE J Allergy Clin Immunol 2006; 117: 1415-8.
49. Forman SB, Garrett AB. Success of omalizumab as monotherapy in adult atopic dermatitis: Case report and discussion of the high-affinity immunoglobulin E receptor, Fcepsilon RI. Cutis 2007; 80: 38-40.
50. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti il-5 recombinant humanised monoclonal antibody for the treatment of atopic dermatitis. Allergy 2005; 60: 693-6.
51. Simon D, Brathen LR, Simon HU. Anti-interleukin-5 antibody therapy in eosinophilic disorders. Pathabiol 2005; 72: 287-92.
52. Prashant S, Dennis PW, Kenneth BG. Biologic Therapy for Psoriasis, The New Therapeutic Frontier. Arch Dermatol 2002; 138: 657-63.
53. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. J Am Acad Dermatol 2002; 46: 1-23.
54. Krueger GG. Current concepts and review of alefacept in the treatment of psoriasis. Dermatol Clin 2004; 22: 407-26.
55. Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN. Alefacept Clinical Study Group. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002; 47: 821-33.
56. Heffernan MP, Hurley MY, Martin KS, Smith DI, Anadkat MJ. Alefacept for alopecia areata. Arch Dermatol 2005; 141: 1513-6.
57. Bui K, Polisetty S, Gilchrist H, Jackson SM, Frederic J. Successful treatment of alopecia universalis with alefacept: a case report and review of the literature. Cutis 2008; 81: 431-4.
58. Foss C, Clark A, Inabinet R, Camacho F, Jorizzo J. An open label pilot study of alefacept for the treatment of pyoderma gangrenosum. J Eur Acad Derm Venerol 2008; 22: 943-9.
59. Richardson S, Getfand J. Immunobiologicals, cytokines and growth factors in dermatology. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's dermatology in general medicine. 7 th ed. McGraw - Hill; 2008. p. 2223-31.
60. Moul DK, Routhouska SB, Robinson MR, Korman NJ. Alefacept for moderate to severe atopic dermatitis: A pilot study in adults. J Am Acad Dermatol 2008; 58: 984-9.
61. Green WH, Leicht SS, Youngberg GA. Patch-stage mycosis fungoides in remission after therapy with alefacept. J Am Acad Dermatol 2008; 58: 110-2.
62. Chang AL, Badger J, Rehmus W. Alefacept for erosive lichen planus: A case series. J Drugs Dermatol 2008; 7: 379-83.
63. Hurd DS, Johnston C, Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). Br J Dermatol 2008; 158: 399-401.
64. Bagel J, Garland WT, Breneman D, Holick M, Littlejohn TW, Crosby D, et al . Administration of DAB389IL-2 to patients with recalcitrant

psoriasis: A double blind, phase II multicenter trial. J Am Acad Dermatol 1998; 3: 938-44.
65. Moreland L, Bate G, Kirkpatrick P. Abatacept. Nat Rev Drug Discov 2006; 5: 185-6.
66. Vincenti F, Kirk AD. What's next in the pipeline. Am J Transplant 2008; 8: 1972-81.
67. Mease PJ, Goffe BS, Metz J, Vander SA, Finck B, Burge DJ. Etanercept in treatment of psoriatic arthritis and psoriasis: A randomized trial. Lancet 2000; 356: 385-90.
68. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al . A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003; 139: 1627-32.
69. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al . Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003; 349: 2014-22.
70. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al . A global Phase III randomized control trial of etanercept in psoriasis: Safety, efficacy and effect of dose reduction. Br J Dermatol 2005; 152: 1304-12.
71. Goldsmith DR, Wagstaff AJ. Etanercept: A review of its use in the management of plaque psoriasis and psoriatic arthritis. Am J Clin Dermatol 2005; 6: 121-36.
72. Yamuchi PS, Gindi V, Lowe NJ. The treatment of psoriasis and psoriatic arthritis with etanercept: Practical considerations on monotherapy, combination therapy and safety. Dermatol Clin 2004; 22: 449-59.
73. Nikas SN, Drosos AA. Onercept. Serono. Curr Opin Investig Drugs 2003; 4: 1369-76.
74. Holman DM, Kallaji AN. Cytokines in dermatology. J Drug Dermatol 2006; 5: 520-4.
75. Oppenheim JJ. Cytokines: Past, present and future. Int J Haematol 2001; 74: 3.
76. Trefzer U, Hofmann M, Sterry W, Asadullah K. Cytokine and anticytokine therapy in dermatology. Expert Opin Biol Ther 2003; 3: 733-43.
77. Thiel DJ, le Du MH, Walter RL, D'Arcy A, Chène C, Fountoulakis M, et al . Observation of an unexpected third receptor molecule in the crystal structure of human interferon-receptor complex. Structure 2000; 8: 927-36.
78. Cac NN, Ballas ZK. Recalcitrant warts, associated with natural killer cell dysfunction, treated with systemic IFN-alpha. J Allergy Clin Immunol 2006; 118: 526-8.
79. Panja SK, Chowdhury A, Banerjee PK, Coondoo A, Nandi S, Saha NC, et al . Interferon Alpha-2b in genital warts. Indian J Dermatol 1991; 36: 5.
80. Rook AH, Kuzel TM, Olsen EA. Cytokine therapy of cutaneous T-cell lymphoma: Interferons, interleukin-12, and interleukin-2. Hematol Oncol Clin North Am 2003; 17: 1435-8.
81. Potthoff A, Brockmeyer NH. HIV-associated Kaposi sarcoma: Pathogenesis and therapy. J Dtsch Dermatol Ges 2007; 5: 1091-4.
82. Kalani AD, Jack A, Montenegro G, Degliuomini J, Wallack MK. Immunotherapy as an adjuvant therapy in the management of advanced, surgically resected melanoma. G Ital Dermatol Venereol 2008; 143: 59-70.
83. Tucker SB, Polasek JW, Perri AJ, Goldsmith EA. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. J Am Acad Dermatol 2006; 54: 1033-8.
84. Edwards L, Berman B, Rapini RP, Whiting DA, Tyring S, Greenway HT Jr, et al . Treatment of cutaneous squamous cell carcinomas by intralesional interferon alpha 2b therapy. Arch Dermatol 1992; 128: 1486-9.
85. Edwards L, Levine N, Widener M. Effect of intralesional alpha 2 interferon on Actinic keratosis. Arch Dermatol 1986; 122: 779.
86. Tsambaos D, Eichelberg D, Goos M. Behçet's syndrome: Treatment with recombinant leucocyte alpha-interferon. Arch Dermatol Res 1986; 278: 335-6.
87. Kim HJ, Colombo M, Frieden IJ. Ulcerated haemangiomas: Clinical characteristics and response to therapy. J Am Acad Dermatol 2001; 44: 962-72.
88. Al-Attar A, Mess S, Thomassen JM., Kauffman CL, Davison SP. Keloid pathogenesis and treatment. Plast Reconstr Surg 2006; 117: 286-300.
89. Gross G, Ikenberg H, Roussaki A, Drees N, Schöpf E. Systemic therapy of condylomata acuminata with recombinant alpha 2a: Low dose superior to the high dose regimen. Chemotherpay 1986; 32: 537-41.
90. Mitchell MS, Abrams J, Thompson JA, Kashani-Sabet M, DeConti RC, Hwu WJ, et al . Randomized trial of an allogeneic melanoma lysate vaccine with low-dose interferon Alfa-2b compared with high-dose interferon Alfa-2b for Resected stage III cutaneous melanoma. J Clin Oncol 2007; 25: 2078-85.
91. Bolinger A, Taeubel MA. Recombinant interferon gamma for treatment of chronic granulomatous disease and other disorders. Clin Pharm 1992; 11; 834-50.
92. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE, et al . Recombinant interferon gamma therapy for Atopic Dermatitis. J Am Acad Dermatol 1993; 28: 189-97.
93. Pierer M, Baerwald C. Biological therapy for the treatment of rheumatic diseases. Internist (Berl) 2008; 49: 938-46.
94. Frischmeyer-Guerrerio PA, Rachamalla R, Saini SS. Remission of Schnitzler syndrome after treatment with anakinra. Ann Allergy Asthma Immunol 2008; 100: 617-9.
95. Ross JB, Finlayson LA, Klotz PJ, Langley RG, Gaudet R, Thompson K, et al . Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up. J Cutan Med Surg 2008; 12: 8-16.
96. Peddle L, Butt C, Snelgrove T. Interleukin (IL) 1alpha, IL1beta, IL receptor antagonist, and IL10 polymorphisms in psoriatic arthritis. Ann Rheum Dis 2005; 64: 1093-4.
97. Marzec M, Halasa K, Kasprzycka M, Wysocka M, Liu X, Tobias JW, et al . Differential effects of interleukin-2 and interleukin-15 versus interleukin-21 on CD4 + cutaneous T-cell lymphoma cells. Cancer Res 2008; 68: 1083-91.
98. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al . High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999; 17: 2105-16.
99. Ghoreschi K, Thomas P, Breit S, Dugas M, Mailhammer R, van Eden W, et al . Interleukin-4 therapy of psoriasis induces Th2 responses and improves human autoimmune disease. Nat Med 2003; 9: 40-6.
100. Trepicchio WL, Ozawa M, Walters IB, Kikuchi T, Gilleaudeau P, Bliss JL, et al . Interleukin-11 therapy selectively down regulates type I cytokine proinflammatory pathways in psoriasis lesions. J Clin Invest 1999; 104: 1527-37.
101. Conti L, Gessani S. GM-CSF in the generation of dendritic cells from human blood monocyte precursors: Recent advances. Immunobiology 2008; 213: 859-70.
102. Chaperot L, Chokri M, Jacob MC, Drillat P, Garban F, Egelhofer H, et al . Differentiation of antigen-presenting cells (dendritic cells and macrophages) for therapeutic application in patients with lymphoma. Leukemia 2000; 14: 1667-77.
103. Meier K, Nanney LB. Emerging new drugs for wound repair. Expert Opin Emerg Drugs 2006; 11: 23-37.
104. Alikhan MA, Carter G, Mehta P. Topical GM-CSF hastens healing of leg ulcers in sickle cell disease. Am J Hematol 2004; 76: 192.
105. Elias EG, Zapas JL, McCarron EC, Beam SL, Hasskamp JH, Culpepper WJ. Sequential administration of GM-CSF (Sargramostim) and IL-2 ± autologous vaccine as adjuvant therapy in cutaneous melanoma: An interim report of a phase II clinical trial. Cancer Biother Radiopharm 2008; 23: 285-91.
106. Bouwhuis SA, Markovic SN, McEvoy MT. Extracorporeal photopheresis and adjuvant aerosolized granulocyte-macrophage colony-stimulating factor for Sézary syndrome. Mayo Clin Proc 2002; 77: 197-200.

107. Pinkas H, Fisch B, Rozansky G, Felz C, Kessler-Icekson G, Krissi H, et al . Platelet-derived growth factors (PDGF-A and -B) and their receptors in human fetal and adult ovaries. Mol Hum Reprod 2008; 14: 199-206.
108. Embil JM, Papp K, Sibbald G. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: An open-label clinical evaluation of efficacy. Wound Repair Regen 2000; 8: 162-8.
109. Asadullah K, Döcke WD, Ebeling M, Friedrich M, Belbe G, Audring H, et al. Interleukin 10 treatment of psoriasis: clinical results of a phase II trial. Arch Dermatol 1999; 135: 187-192.
110. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, et al. British association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol 2005; 153: 486-97.
111. Sterry W, Barker J, Boehncke WH, Bos JD, Chimenti S, Christophers E, et al. Biological therapies in the systemic management of psoriasis: International Consensus Conference. Br J Dermatol 2004; 151: 3-17.
112. Koo J, Khera P. Update on the mechanisms and efficacy of biological therapies for psoriasis. J Dermatol Sci 2005; 38: 75-87.
113. Asadullah K, Sterry W, Ebeling M, Friedrich M, Leupold M, Jasulaitis D, et al. Clinical and immunological effects of IL-10 therapy in psoriasis. Br J Dermatol 1999; 141: 989.
114. Sukal SA, Nadiminti L, Granstein RD. Etanercept and demyelinating disease in a patient with psoriasis. J Am Acad Dermatol 2006; 54: 160-4.
115. Scheinfeld N. Adalimumab: A review of side effects. Exp Opin Drug Saf 2005; 4: 637-41.
116. Thappa DM, Laxmisha C. Immunomodulators in the treatment of Psoriasis. Indian J Dermatol Venereol Leprol 2004; 70: 1-9.
117. Lebowhl M, Clark LN. Recent advances in medical dermatology. Int J Dermatol 2007; 1: 197-202.
118. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British association of dermatologist guidelines for biological intervention for psoriasis 2009.Br J Dermatol 2009; 161: 987-1019.

Case Report

BJMP 2013;6(4):a631

Bortezomib induced reversible left ventricular systolic dysfunction: A case report and review of literature

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Abstract

Bortezomib is a reversible proteasome inhibitor, currently approved by US FDA for use in multiple myeloma and mantle cell lymphoma. Bortezomib has been shown to cause new onset and exacerbation of underlying congestive cardiac failure (CHF) in some case reports. Studies on human tissue have shown dysregulation of ubiquitin proteasome system (UPS) in cardiac tissues in end stage heart failure. Recently, an animal study has shown reduced left ventricular contractility after bortezomib administration, which was attributed to reduced ATP synthesis in mitochondria of cardiac myocytes.

Our case demonstrates development of new onset severe reversible left ventricular systolic dysfunction after 4 cycles of bortezomib in a 58 year old female with multiple myeloma. Her only medical condition was well controlled hypertension and she did not have any other risk factor for coronary artery disease. We also present a review of all case reports of CHF associated with bortezomib administration published till date and occurrence of CHF with bortezomib administration in major clinical trials of multiple myeloma.

Our manuscript highlights the importance of maintaining a high level of suspicion for development of CHF after therapy with bortezomib. Currently, there is no guideline for routine evaluation and monitoring of cardiac function in all patients during the course of bortezomib therapy. Further studies are required in future to address this issue.

Keywords: Bortezomib, Congestive heart failure, Ubiquitin proteasome system.

Introduction

Bortezomib is a reversible proteasome inhibitor, currently approved by US FDA for use in multiple myeloma and mantle cell lymphoma. It has been shown to cause new onset and exacerbation of underlying congestive cardiac failure (CHF) in some case reports. Although the exact mechanism of bortezomib induced congestive cardiac failure is unknown, studies have shown dysregulation of ubiquitin proteasome system (UPS) in human cardiac tissues in end stage heart failure[1-3]. Furthermore, a study in rats has shown reduced left ventricular contractility after bortezomib administration, which was attributed to reduced ATP synthesis in mitochondria of cardiac myocytes[4]. Our case demonstrates new onset severe reversible left ventricular systolic dysfunction after 4 cycles of bortezomib in a 58 year old female with multiple myeloma. It highlights the importance of monitoring cardiac function in patients receiving bortezomib.

Case Report

A 58 year old female with past medical history of well controlled hypertension presented with severe low back pain, anorexia and unintentional weight loss of around 20 pounds over a period of 3 months in medical clinic. On evaluation of her routine laboratory tests, she was found to have haemoglobin of 6.5 g/dl, haematocrit of 19.9%, white blood cell (WBC) count of 3.9 x 10^3/cc, red blood cell (RBC) count of 2.18 x 10^6/cc and platelet count of 1.52 x 10^5/cc. Her blood urea nitrogen and creatinine was 10 mg/dl and 0.7 mg/dl respectively and corrected calcium level was 10g/dl. On liver function test, her total protein was 12.4 g/dl and albumin level was 2.8 g/dl. X-ray of lumbosacral spine revealed a compression fracture at the level of T12and L2 vertebra. Bone survey confirmed diffuse osteopenia, severe collapse of the body of T12 and partial collapse of L2 and L3. Due to the presence of severe anaemia and compression fractures, multiple myeloma was suspected. Urine protein electrophoresis showed two monoclonal protein bands with concentration of 46.8% and 4.8% and urine immunofixation showed two intact monoclonal IgA-Kappa immunoglobulin bands. Beta-2 microglobulin level was 5.49. Bone marrow aspiration and biopsy confirmed the diagnosis of multiple myeloma. Patient was staged as IIIA according to Durie-Salmon staging system.

Subsequently, patient was planned to be treated with eight cycles of bortezomib and dexamethasone, with bortezomib being given on day 1, 4, 8 and 11 of each cycle at a dose of 1.3 mg/m^2 body surface area. Prior to initiation of chemotherapy, she received radiotherapy to spine as well. However, after completing the fourth cycle of bortezomib/dexamethasone, she was admitted to the hospital with generalized weakness, nausea and vomiting. Chest X ray revealed possible right lower lobe infiltrate or effusion along with increased bronchovascular markings and she was treated with antibiotics for suspected community acquired pneumonia. However, an echocardiogram was obtained due to bilateral crackles on physical exam and increased bronchovascular markings on chest X ray, which revealed dilation of left ventricle with left ventricular ejection fraction of 30-35%, diffuse hypo kinesis of left ventricle, mild mitral and tricuspid regurgitation and diastolic dysfunction

with abnormal relaxation(Tajik grade I). Left ventricular septal and posterior wall thickness was 0.8 cm. Infiltrative Cardiomyopathy in the setting of multiple myeloma was unlikely due to the absence of bi-atrial enlargement, pericardial effusion and thick bright myocardium on echocardiogram. Cardiology consultation was sought and their impression was new onset left ventricular dysfunction due to bortezomib therapy.

Patient did not receive any further cycles of chemotherapy due to cardiotoxicity and was on optimal medical management for heart failure with lisinopril, carvedilol and isosorbide dinitrate. An echocardiogram was repeated four months after discontinuation of bortezomib, which revealed normal left ventricular contractility with global left ventricular ejection fraction of 55% and trace mitral regurgitation.

Currently, at 2 year follow up, her echocardiogram shows global left ventricular ejection fraction of 65%, trace mitral and tricuspid regurgitation and diastolic dysfunction with abnormal relaxation(Tajik grade I).

Discussion and Review of Literature

Botezomib is a novel proteasome inhibitor which acts by inducing bcl-2 phosphorylation and cleavage, resulting in G2-M cell cycle phase arrest and apoptosis[5]. US Food and Drug Administration (FDA) have approved bortezomib for use in multiple myeloma and mantle cell lymphoma. The common adverse effects of bortezomib observed in clinical trials and post marketing surveillance include thrombocytopenia, neutropenia, hypotension, asthenia, peripheral neuropathy and nausea. US package insert for bortezomib states that acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction and it is recommended to closely monitor patients with risk factor for, or existing heart disease.

The role of ubiquitin proteasome system (UPS) in heart failure has been studied extensively in recent years. Two studies by Hein et al and Weekes et al in 2003 have shown presence of increased amount of ubiquitinated proteins and substrates in cardiac tissues of heart failure patients, indicating reduced activity of UPS in end stage heart failure[1-3]. Another study has shown impaired proteasome activity in hypertrophic and dilated cardiomyopathy likely secondary to post translational modification of proteasome[6].However, in early stage heart failure, there is increased activity of UPS, resulting in remodelling and high cardiac output[2]. Bortezomib, by inhibiting UPS, would lead to accumulation of ubiquitinated proteins in cardiac myocytes, similar to that seen in end stage heart failure. A study in rats exposed to bortezomib alone showed development of left ventricular systolic dysfunction by echocardiography and reduced synthesis of ATP was observed in the mitochondria of cardiac myocytes[4]. However, the exact mechanism of bortezomib induced systolic dysfunction in humans is not clear.

There have been a few reported cases of bortezomib induced congestive cardiac failure in literature (Table 1). The amount of bortezomib administered before development of symptoms of heart failure was 20.8 mg/m^2 in four patients, 3 mg/m^2 in one patient and 10.4mg/m^2 in one patient. Three of them have received prior anthracycline based chemotherapy. Complete reversibility of heart failure after discontinuation of bortezomib was documented only in two cases by follow up echocardiograms and brain natriuretic peptide levels[7, 8]. The patient described in our index case had well controlled hypertension and no additional cardiac risk factors at baseline. She developed non-specific symptoms, including weakness, nausea and vomiting after the fourth cycle of chemotherapy and was admitted to the hospital for community acquired pneumonia. However, an echocardiogram was obtained due to pulmonary congestion, which uncovered the diagnosis of left ventricular systolic failure. The two echocardiograms obtained at a follow up of 4 months and 2 years showed gradual improvement in ejection fraction to 55% and 65% respectively from 15% after chemotherapy with bortezomib.

We did a review of major clinical trials of bortezomib in patients with multiple myeloma, Waldenstrom's macroglobulinemia and plasma cell leukaemia (Table 2) to investigate the incidence of congestive cardiac failure reported after administration of bortezomib. In APEX trial, the incidence of congestive cardiac failure was 2% in both bortezomib and high dose dexamethasone group [11]. In a study on melphalan refractory multiple myeloma by Hjorth et al, 3 cases of congestive cardiac failure was reported in bortezomib-dexamethasone group and 2 cases were reported in thalidomide-dexamethasone group[12]. Another study evaluating the safety of prolonged therapy with bortezomib by Berenson et al reported 1 case of cardiomegaly and 1 case of pulmonary edema[13]. However, further studies are needed to specifically evaluate the incidence of congestive cardiac failure with bortezomib therapy.

In summary, our case and review highlights the importance of maintaining a high level of suspicion for development of congestive cardiac failure after therapy with bortezomib. Given the widespread use of bortezomib and new generation proteasome inhibitors in multiple myeloma, there might be increased incidence of new onset and exacerbation of underlying congestive cardiac failure in future. Currently, there is no guideline for routine evaluation and monitoring of cardiac function in all patients during the course of bortezomib therapy. Furthermore, it is unclear whether the severity of congestive cardiac failure is proportional to the cumulative dosage of bortezomib administration and also, if there is any correlation between onsets of congestive cardiac failure with the timing of bortezomib therapy. Further studies are required in future to address these issues.

Table 1: Review of cases of bortezomib induced congestive cardiac failure reported so far.

Author	Age/sex	Prior cardiac history and risk factors	Baseline cardiac function	Number of Bortezomib containing cycles	Exposure to other cardiotoxic medications	Amount of Bortezomib received before onset of cardiac symptoms	Lowest EF** after Bortezomib administration	EF on follow up visits
Voortman et al[7]	53/M	36 pack years of smoking and COPD	Echo not available; NT-Pro BNP 1389 ng/l	4	Gemcitabine	3 mg/m^2	10-15% on Echo after 4 cycles	45% on MUGA scan at 6 months
Orciuolo et al[9]	73/M	NK*	NK	6	1 Anthracycline containing regimen	20.8 mg/m^2	EF 25%	NK
Orcioulo et al[9]	61/F	NK	NK	4	2 Anthracycline containing regimens	20.8 mg/m^2	EF 20%	NK
Orciuolo et al[9]	80/F	NK	NK	4	1 prior non anthracycline chemotherapy regimen received	20.8 mg/m^2	EF 35%	NK
Hasihanefioglu et al[10]	47/M	None	EF 70% and normal coronary angiogram	2	1 cycle of Vincristine, Doxorubicin and Dexamethasone	10.4 mg/m^2	EF 10%	EF 20% at 6 month follow up
Bockorny et al[8]	56/F	Hypertension, well controlled	NK	4	None	20.8 mg/m^2	EF 20-25%	EF 55-60%
INDEX CASE	58/F	Hypertension, well controlled	NK	4	None	20.8 mg/m^2	EF 30-35%	EF 55% at 4 month and 65% at 2 year follow up.

*NK: Not Known; **EF: Ejection Fraction

Table 2: Review of cases of congestive cardiac failure reported in clinical trials with bortezomib in multiple myeloma, Waldenström's Macroglobulinemia and plasma cell leukaemia.

Authors (ref)	Study	Study population	Significant Cardiac events (n)
Berenson, J.R. et al. 2005[13]	Safety of prolonged therapy with bortezomib in relapsed or refractory multiple myeloma	63 patients with relapsed and/or refractory MM	Cardiomegaly (1) MI, SVT, Pulmonary oedema (1) Complete AV block (1)
Chen, C.I. et al. 2007[14]	Bortezomib in Waldenström's Macroglobulinemia	27 patients with untreated or relapsed WM	Congestive Heart Failure (1)
D'Arena, G. et al. 2012[15]	Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukaemia	29 patients with untreated PPCL	None reported
Hjorth, M. et al. 2012[12]	Thal-Dex vs. Bort-Dex in refractory myeloma	131 patients with Melphalan refractory MM	2 cases of cardiac failure in Thal-Dex group and 3 in Bort-dex group

Jagannath, S. et al 2009[16]	Bortezomib for Relapsed or Refractory Multiple Myeloma	54 patients with relapsed or refractory MM	None reported
Jagannath, S. et al 2010[17]	Extended follow-up of Frontline Bortezomib ± Dexamethasone for MM	49 patients with untreated MM	None reported
Kobayashi, T. et al. 2010[18]	Bortezomib plus dexamethasone for relapsed or treatment refractory multiple myeloma	88 patients with relapse/refractory MM	None reported
Mikhael, J.R. et al. 2009[19]	High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma	638 patients with refractory or relapsed MM	None reported
Richardson, P.G. et al. 2003[20]	A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma	202 patients with relapsed MM	None reported
Richardson, P.G. et al. 2005[11]	Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma(APEX trial)	669 patients with relapsed MM	Congestive cardiac failure in 2% of each arm.
Rosino, L. et al. 2007[21]	Phase II PETHEMA Trial of Alternating Bortezomib and Dexamethasone As Induction Regimen Before Autologous Stem-Cell Transplantation in Younger Patients With Multiple Myeloma	40 patients with newly diagnosed MM	None reported
Sonneveld, P. et al. 2012[22]	Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma	827 patients with newly diagnosed MM	Cardiac Disorders in 5% of patient in VAD group vs. 8% of patients in PAD group.
Yuan, Z.G. et al. 2011[23]	Different dose combinations of bortezomib and dexamethasone in the treatment of relapsed or refractory myeloma	168 patients with relapsed MM	None reported
Suvannasankha et al 2006[24]	Weekly bortezomib/methylprednisolone in relapsed multiple myeloma	29 patients with relapsed multiple myeloma	1 case of congestive cardiac failure

Conclusion

CHF is an infrequent but serious adverse effect of bortezomib. Cardiac function should be closely monitored in patients receiving bortezomib, as case reports have shown that these patients might present with non-specific symptoms like weakness and fatigue. Further studies are required to establish the frequency and mode of monitoring of cardiac function during and after bortezomib therapy.

Competing Interests
None.
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REFERENCES

1. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: Structural deterioration and compensatory mechanisms. Circulation. 2003; 107(7):984-991.
2. Powell SR, Herrmann J, Lerman A, Patterson C, Wang X. The ubiquitin-proteasome system and cardiovascular disease. Prog Mol Biol Transl Sci. 2012;109:295-346. doi: 10.1016/B978-0-12-397863-9.00009-2; 10.1016/B978-0-12-397863-9.00009-2.
3. Weekes J, Morrison K, Mullen A, Wait R, Barton P, Dunn MJ. Hyperubiquitination of proteins in dilated cardiomyopathy. Proteomics. 2003;3(2):208-216. doi: 10.1002/pmic.200390029.
4. Nowis D, Maczewski M, Mackiewicz U, et al. Cardiotoxicity of the anticancer therapeutic agent bortezomib. Am J Pathol. 2010;176(6):2658-2668. doi: 10.2353/ajpath.2010.090690; 10.2353/ajpath.2010.090690.
5. Ling YH, Liebes L, Ng B, et al. PS-341, a novel proteasome inhibitor, induces bcl-2 phosphorylation and cleavage in association with G2-M phase arrest and apoptosis. Mol Cancer Ther. 2002;1(10):841-849.
6. Predmore JM, Wang P, Davis F, et al. Ubiquitin proteasome dysfunction in human hypertrophic and dilated cardiomyopathies. Circulation. 2010;121(8):997-1004. doi: 10.1161/CIRCULATIONAHA.109.904557; 10.1161/CIRCULATIONAHA.109.904557.
7. Voortman J, Giaccone G. Severe reversible cardiac failure after bortezomib treatment combined with chemotherapy in a non-small cell lung cancer patient: A case report. BMC Cancer. 2006;6:129. doi: 10.1186/1471-2407-6-129.
8. Bockorny M, Chakravarty S, Schulman P, Bockorny B, Bona R. Severe heart failure after bortezomib treatment in a patient with multiple myeloma: A case report and review of the literature. Acta Haematol. 2012;128(4):244-247. doi: 10.1159/000340050; 10.1159/000340050.
9. Enrico O, Gabriele B, Nadia C, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. Br J Haematol. 2007;138(3):396-397. doi: 10.1111/j.1365-2141.2007.06659.x.
10. Hacihanefioglu A, Tarkun P, Gonullu E. Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib. Int J

Hematol. 2008;88(2):219-222. doi: 10.1007/s12185-008-0139-7; 10.1007/s12185-008-0139-7.
11. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-2498. doi: 10.1056/NEJMoa043445.
12. Hjorth M, Hjertner O, Knudsen LM, et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: A randomized study. Eur J Haematol. 2012;88(6):485-496. doi: 10.1111/j.1600-0609.2012.01775.x; 10.1111/j.1600-0609.2012.01775.x.
13. Berenson JR, Jagannath S, Barlogie B, et al. Safety of prolonged therapy with bortezomib in relapsed or refractory multiple myeloma. Cancer. 2005;104(10):2141-2148. doi: 10.1002/cncr.21427.
14. Chen CI, Kouroukis CT, White D, et al. Bortezomib is active in patients with untreated or relapsed waldenstrom's macroglobulinemia: A phase II study of the national cancer institute of canada clinical trials group. J Clin Oncol. 2007;25(12):1570-1575. doi: 10.1200/JCO.2006.07.8659.
15. D'Arena G, Valentini CG, Pietrantuono G, et al. Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: A retrospective study from GIMEMA multiple myeloma working party. Ann Oncol. 2012;23(6):1499-1502. doi: 10.1093/annonc/mdr480; 10.1093/annonc/mdr480.
16. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004;127(2):165-172. doi: 10.1111/j.1365-2141.2004.05188.x.
17. Jagannath S, Durie BG, Wolf JL, et al. Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma. Br J Haematol. 2009;146(6):619-626. doi: 10.1111/j.1365-2141.2009.07803.x; 10.1111/j.1365-2141.2009.07803.x.
18. Kobayashi T, Kuroda J, Shimura K, et al. Bortezomib plus dexamethasone for relapsed or treatment refractory multiple myeloma: The collaborative study at six institutes in kyoto and osaka. Int J Hematol. 2010;92(4):579-586. doi: 10.1007/s12185-010-0696-4; 10.1007/s12185-010-0696-4.
19. Mikhael JR, Belch AR, Prince HM, et al. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: Results of a global phase 3b expanded access program. Br J Haematol. 2009;144(2):169-175. doi: 10.1111/j.1365-2141.2008.07409.x; 10.1111/j.1365-2141.2008.07409.x.
20. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348(26):2609-2617. doi: 10.1056/NEJMoa030288.
21. Rosinol L, Oriol A, Mateos MV, et al. Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: Efficacy and clinical implications of tumor response kinetics. J Clin Oncol. 2007;25(28):4452-4458. doi: 10.1200/JCO.2007.12.3323.
22. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30(24):2946-2955. doi: 10.1200/JCO.2011.39.6820; 10.1200/JCO.2011.39.6820.
23. Yuan ZG, Jin J, Huang XJ, et al. Different dose combinations of bortezomib and dexamethasone in the treatment of relapsed or refractory myeloma: An open-label, observational, multi-center study in china. Chin Med J (Engl). 2011;124(19):2969-2974.
24. Suvannasankha A, Smith GG, Juliar BE, Abonour R. Weekly bortezomib/methylprednisolone is effective and well tolerated in relapsed multiple myeloma. Clin Lymphoma Myeloma. 2006;7(2):131-134. doi: 10.3816/CLM.2006.n.050.

Case Report

BJMP 2013;6(4):a630

Aggression and Homicidal Thoughts in a Patient with Primary Hyperparathyroidism: A Case Report

John Otasowie and Billy-Anne Hambleton

Abstract

Introduction: Aggression in various forms may be one of the components of emotional/behavioural problems seen in a Child and Adolescent Mental Health Service. Aggressive symptoms may result from a psychiatric condition or a physical illness such as Primary Hyperparathyroidism.

Case Presentation: The authors present a case of worsening psychiatric symptoms in a patient who was serendipitously diagnosed with Primary Hyperparathyroidism. His aggressive outbursts, suicidal and homicidal thoughts remitted following parathyroidectomy.

Conclusion: Primary Hyperparathyroidism should be considered in the differential diagnosis in young people with worsening neuropsychiatric symptoms which are unresponsive to standard psychiatric treatment. Child Psychiatrists should always take holistic approach when managing patients and should be familiar with medical conditions that present with psychiatric symptoms.

Keywords: Key words: Aggression, primary hyperparathyroidism.

Abbreviations: Abbreviations: PHPT – primary hyperparathyroidism; CAMHS – Child and Adolescent Mental Health Service; GP – General Practitioner; FBC – Full Blood Count; LFT – Liver Function Test; U&E – Urea and Electrolytes; TFT – Thyroid Function Test.

Introduction:

We report a case of worsening psychiatric symptoms in a patient who was serendipitously diagnosed with Primary Hyperparathyroidism.

Behavioural change in form of aggression sometimes occurs as a component of psychiatric disorders such as psychosis, attention deficit hyperactivity disorder, autistic spectrum condition, conduct disorder and various mood disorders. It may also present as a psychiatric manifestation of an endocrine disorder such as Primary Hyperparathyroidism (PHPT)[1,2].

PHPT is rare in children and adolescents with an incidence of 2-5 in 100000[3]. It is characterized by hypercalcaemia and elevation of parathyroid hormone. Children with PHPT may present with non-specific complaints such as behavioural change and deteriorating school performance.

Patients who present with non-renal symptoms have a longer duration of symptoms prior to diagnosis of PHPT[4,6]. It seems probable that it takes much longer for diagnosis to be made in those with pre-existing mental disorder. When left undiagnosed and untreated, PHPT can be a serious disease with significant morbidity.

The finding of elevated serum calcium levels in young people is often fortuitous as they often present with non-specific symptoms[3,4]. A significant number of hyperparathyroidism cases with neuropsychiatric manifestation have been reported in patients without recorded pre-existing psychiatric diagnosis [3-6].

This case report highlights the need for clinicians to always consider endocrine disorder as a differential diagnosis when treating patients with psychiatric symptoms which are poorly responsive to standard treatment. It also demonstrates the relevance of an integrated approach in healthcare delivery including the importance of good communication between primary and tertiary care clinicians.

Case Report:

A 15yr old Caucasian male known to Child & Adolescent Mental Health Service (CAMHS) for management of his behavioural problems presented in crisis as a consequence of physical aggression, suicidal ideation and homicidal thoughts.

His first contact with CAMHS had been at the age of 10 when he was referred for management of his frequent aggressive outbursts. He had always been boisterous but had no previous history of significant emotional or behavioural difficulties. His developmental history was unremarkable and there were no features indicative of any neurodevelopmental disorder. There was no family history of mental illness.

His biological parents were involved in an acrimonious divorce at the time of his first referral to CAMHS so it was felt that this conflict may have contributed to his presentation.

He was referred a Child Psychotherapist for weekly sessions as the initial assessment suggested significant weakness in his attachment and identification which manifested in the instability and immaturity of mood and behaviour.

The family described minimal improvements in his capacity for self-control having had three years of psychotherapy. His behaviour remained challenging but manageable within the community until six months prior to him being re-referred by his General Practitioner (GP) for urgent psychiatric assessment.

Following parental divorce, his mum remarried but her new marriage was also turbulent and the couple had to separate. During this period of increased psychosocial stresses within his family, the patient's behaviour escalated to a point that he was regarded as a significant risk to himself and others. It was thought that the separation between his mother and step-father might have triggered this deterioration.

The night before his urgent referral to CAMHS, he set a trap for his mother; he had put a rope around some curtains on the floor and was planning to throw another curtain over her. He also had a knife and hockey stick with him at the time. As his mother stepped into the room, he put the curtain over her head and attempted to hit her with the hockey stick. He was promptly restrained by his father, who had come to visit, before he could do much damage.

He presented as unpredictable and aggressive but would often deny recollection of any reported outbursts. He was very upset when incidents were talked about as he believed he had no control whatsoever over this behaviour – it was clear how upsetting his behaviour was to *him*.

He displayed uncontrollable rage on many occasions. It was usually directed at his mother and home furniture, and might last up to two hours. He appeared to seek immediate gratification and was clearly hypersensitive to his setting with a significant degree of paranoia and irritability.

He repeatedly stated that he had thoughts of wanting to kill his mother and himself especially when angry. He did not appear able to accept any responsibility for his actions, blaming his temper outbursts on his older sibling. We heard she was extremely frightened of him; he had on two occasions broken down her door.

When he came out of these rages he would become very tearful and profoundly apologetic. These difficulties had been noticed at school where his grades had been falling. He told teachers he felt suicidal and would sometimes go into the school toilet to cry especially when he thought about his inability to control himself.

Physical examination at this point was unremarkable. The Community Psychiatrist commenced him on Fluoxetine and referred him to an in-patient psychiatric unit for further psychiatric evaluation including a forensic assessment.

He was diagnosed with Asperger's Syndrome and Attention Deficit Hyperactivity Disorder in the inpatient unit and was prescribed risperidone and methylphenidate. His GP was asked to arrange a baseline blood test, consisting of full blood count (FBC), liver function test (LFT), urea & electrolytes (U&E) and thyroid function test (TFT). There was no request for blood glucose level or serum calcium.

The GP asked for a serum calcium level estimate purely out of 'habit'. The laboratory result showed a high level of calcium 3.89mmol/L (normal range 2.2-2.6). Based on this significantly elevated serum calcium level, a referral was sent to the Paediatric Endocrinologist.

At the Endocrinology Clinic, he described a twelve month history of generalised aches and pains in association with emotional lability. A history of fracture of his right wrist and left hallux occurring within 18 months prior to presentation was also obtained. The X-ray report showed presence of a radiolucent area in his right femur. An assay of his parathyroid hormone, Sestamibi scan and ultrasound scan of his neck were done.

The elevated parathyroid hormone level, increased serum calcium, history of fractures and X-ray features indicated the diagnosis of Primary Hyperparathyroidism. The endocrinologist was of the opinion that his PHPT has been present for a number of years. He was referred for parathyroidectomy.

His serum calcium level dropped to 2.47mmol/L two days post-surgery. As calcium level normalised, his symptoms improved remarkably and his psychotropic medications were discontinued. Since then, he has successfully commenced college full time and has succeeded in obtaining good grades in his chosen courses.

Discussion:

Psychiatric symptoms cause significant impairment in children and adolescents. Having additional symptoms of hyperparathyroidism would exacerbate the psychiatric symptoms and increase the degree of impairment. This patient presented with neuropsychiatric symptoms and evidence of end organ damage which is similar to those in published reports[3,4].

Research shows that diagnosis of primary hyperparathyroidism is often delayed in young people but we suspect that it may even be more delayed in those with a pre-existing psychiatric disorder as the symptoms may be more likely to be attributable to the psychiatric condition.

It is possible that the behavioural problems in this patient may have co-existed independently of each other, but the rapid resolution of the psychiatric symptoms suggests that they may have been exacerbated by hyperparathyroidism.

Our findings in this case are similar to those reported by Spivak and colleagues' which showed that early diagnosis of hypercalcaemia can prevent unnecessary and potentially harmful treatment with psychotropic medications[7].

Psychiatric diagnoses are usually formed from identification of collective symptoms some of which may occur in other medical conditions. Adopting a multidisciplinary team approach is most helpful in the management of complex psychiatric cases. This approach may encourage clinicians to take a holistic view in management of children.

It is important for clinicians to be familiar with common psychiatric symptoms and medical conditions that may mimic or cause them because the presence of non-specific symptoms in PHPT poses a significant emotional burden for affected children and their families. It is a potentially treatable condition which if not diagnosed early could lead to impaired psychosocial well-being and damage of vital organs. Parathyroidectomy has been shown to improve general health, quality of life and cognitive functioning in patients with PHPT[8].

The outcome for this particular young person could have included further episodes of in-patient hospitalisation or involvement with the juvenile justice system as a consequence of further violent episodes. The achievement of adolescent milestones and his education could have been severely disrupted and may have resulted in labelling detrimental to his future.

In the current economic climate and because of the rarity of Primary Hyperparathyroidism, we do not advocate routine serum calcium estimation in all behavioural problems but clinicians should have lower threshold for screening for this condition especially in patients with worsening symptoms despite conventional treatment.

In conclusion, Primary Hyperparathyroidism should be considered in the differential diagnosis in young people with worsening neuropsychiatric symptoms which are unresponsive to standard psychiatric treatment.

Competing Interests
None declared
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REFERENCES

1. Velasco PJ, Manshadi M, Breen K, Lippmann S. Psychiatric Aspects of Parathyroid Disease. Psychosomatics. 1999; 40: 486-490
2. Gatewood JW, Organ CH, Mead BT. Mental changes associated with hyperparathyroidism. Am J Psychiatry. 1975; 132: 129-132
3. Kollars J, Zarroung AE, van Heerden J, Lteif A, Stavlo P, Suarez L, Moir C, Ishitani M, Rodeberg D. Primary hyperparathyroidism in paediatric patients. Paediatrics. 2005; 115: 974-980
4. Lawson ML, Ellis G, Filler RM, Kooh SW. Primary hyperparathyroidism in a paediatric hospital. Quarterly Journal of Medicine. 1996; 89: 921-932
5. Bjernulf A, Hall L, Sjogran I, Werner I. Primary hyperparathyroidism in children. Brief review and case report. Acta Paediatrica Scandinavica. 1970; 59: 249-258
6. Hsu SC, Levine MA (). Primary hyperparathyroidism in children and adolescents: the John Hopkins Children's Centre experience 1984-2001. J Bone Miner. 2002; Res.17(suppl 2): N44-N50
7. Spivak B, Radvan M, Ohring R, Weizman A. Primary hyperparathyroidism, psychiatric manifestations, diagnosis and management. Psychother Psychosom 1989; 51(1): 38-44
8. Coker LH, Rorie K, Cantley L et al. Primary hyperparathyroidism, cognition, and health-related quality of life. Annals of Surgery 2005; 242(5): 642-650

Case Report

BJMP 2013;6(4):a627

Guttate psoriasis: A rare cause of diffuse rash.

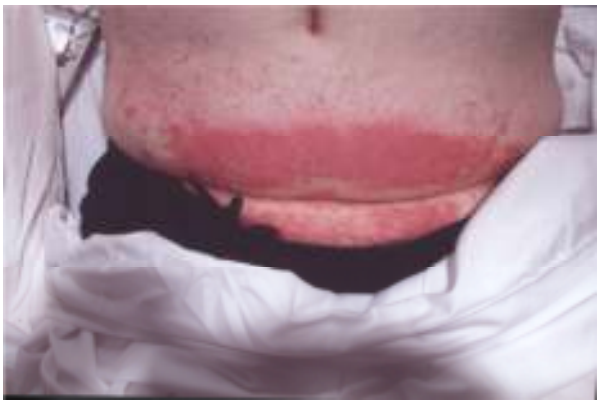
Nauman Shahid, Muhammad Z Bawany, Ehsan Rafiq and Thomas Sodeman

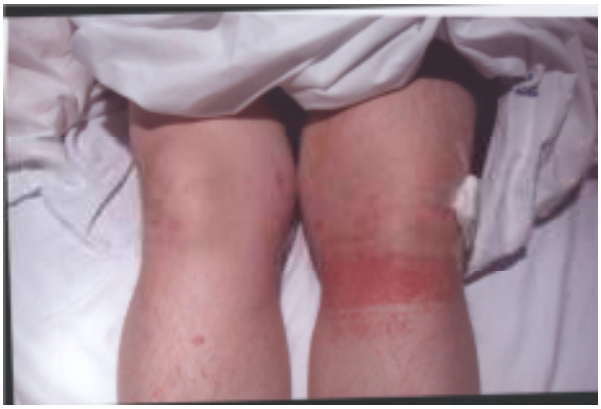
Abstract
Guttate psoriasis is a variant of psoriasis presenting as small, erythematous papules and plaques on the skin. Streptococcal infection is a common inciting factor. We are reporting a case of a 53 years old male, who presented with a generalized rash without any history of a recent infection and was diagnosed with guttate psoriasis on skin biopsy.

Introduction

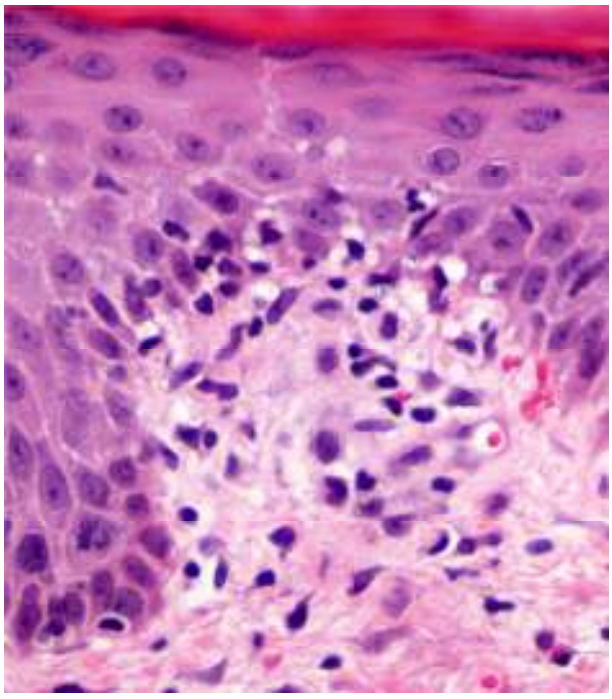
Psoriasis is a common skin disorder characterized by erythematous papules and plaque formation with silver scaling. Guttate psoriasis is much less common and many studies cite a prevalence of less than 30% among patients who have psoriasis. It refers to the acute appearance of multiple skin eruptions mostly in a patient with no preexisting psoriasis and less commonly in a patient with psoriasis. We report here a case of guttate psoriasis associated with a flare of psoriatic arthritis.

Case report



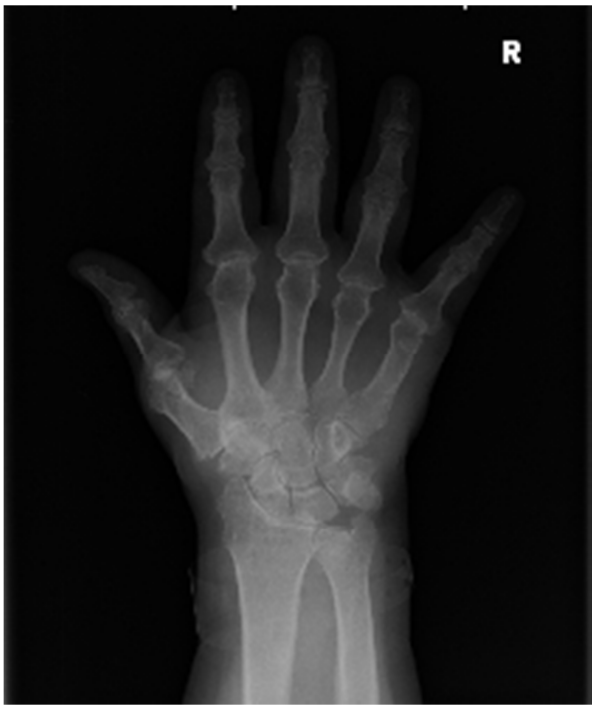


A 53 year old man presented with a generalized body rash and multiple joint pains. His symptoms started a week prior to presentation. The skin rash initially appeared on his back and flanks but gradually progressed to involve the thighs and arms. He had 'sausage fingers', bilateral knee and ankle swelling associated with pain and sporadic metatarsophalyngeal joint pain as manifestations of his arthritis.



His past medical history included hypertension, diabetes mellitus, hyperlipidemia and psoriasis with psoriatic arthritis. He did not report any recent changes in his medication. The patient denied any history of fever, sore throat, weight loss, visual problems, dyspnea, cough, gastrointestinal complaints or recent travel. Physical examination revealed a diffuse, non-blanching, pruritic, maculopapular and maculopustular rash over the trunk. He also had a scaly and diffuse erythematic rash over the lower abdomen which was non-blanching and pruritic. Auspitz's sign was positive. He had multiple painful joints including both knees, right wrist, left proximal interphalangeal joint, and both his ankles. Left knee arthrocentesis was done

which revealed joint fluid consistent with inflammatory joint disease without any evidence of crystals. Laboratory tests, including red and white blood cell count, haemoglobin, cyclic citrullinated peptide antibody, rapid plasma regain, hepatitis panel, antinuclear antibody, rheumatoid factor, lyme markers and serum uric acid revealed no abnormalities. ASO titer level was positive at 196. An x-ray of his left hand showed periarticular erosive changes along the distal aspect of the proximal phalanx. A skin biopsy was performed which revealed mild spongiosis and a perivascular lymphoplastic infiltrate. A diagnosis of guttate psoriasis was made. He was started on prednisone, methotrexate and folic acid and discharged from hospital. He was followed up in the rheumatology clinic 2 weeks after discharge and his rash had improved.



Discussion

Unlike psoriasis, guttate psoriasis is a much lesser known entity. It refers to the acute appearance of multiple skin eruptions, mostly in patients with no preexisting psoriasis and less commonly in chronic plaque psoriasis (guttate flare of chronic plaque psoriasis).

The characteristic skin lesions of guttate psoriasis are less than 1 cm in diameter, hence the name guttate (drop like). The lesions look like a shower of red, scaly tear drops that have fallen down on the body mainly involving the trunk, arms, thighs and face. Guttate psoriasis should be differentiated from diabetic dermopathy, also called shin spots, which typically begin as dull red, scaly papules or plaques and later develop into bilateral asymmetrical circumscribed shallow pigmented scars and/or brownish macular lesions with a fine scale. In diabetic dermopathy the lesions usually are greater than 4 cm in size.

Diagnosis is usually made on clinical examination; however skin biopsy is helpful in difficult cases. Histopathologic findings of guttate psoriasis vary with the age of the lesion. Findings in early lesions may be nonspecific and may include mild acanthosis, papillary dermal oedema and lymphocyte-predominant dermal infiltrate. Mature lesions exhibit parakeratosis alternating with hyperkeratosis, epidermal acanthosis, Munro microabscesses and dermal perivascular infiltrate containg neutrophils, lymphocytes and macrophages.

Streptococcal infections are well known to precipitate guttate psoriasis,[1] however there have been no significant improvements in patients who were given penicillin or erythromycin when compared to those who were not treated.[2] Other known precipitants are physical and psychological trauma.

The exact pathophysiologic mechanism is undetermined. The disease is believed to result from an immune reaction triggered by a previous streptococcal infection in a genetically susceptible host. Recent research points toward chromosome 6 as HLA-Cw*0602 allele positive patients are more prone to develop the guttate form.

Competing Interests
None declared
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REFERENCES

1. The role of streptococcal infection in initiation of Guttate Psoriasis ., Telfer ,Chalmer . Arch Dermatol 1992 Jan ;128 : 39-42 (Telfer NR, Chalmers RJG, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol. 1992;128:39-42)
2. Antistreptococcal treatment of guttate psoriasis: a controlled study.Dogan B, Karabudak O, Harmanyeri Y. Int J Dermatol. 2008 Sep;47(9):950-2.