MedPrecis
Never Stop Exploring

Journal of Clinical Oncology and Cancer Research
Volume 1, Issue 1

Research Article | Open Access

Multiple Myeloma: Bortezomib, Lenalidomide, and Dexamethasone Intensol

López Anglada[1*], Juan Bargay[2], Isidro Jarque[2], Ana González[3], Bruno Paiva[4]

[1]Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer y Centro Regional de Hemodonación, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain

[2]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

[3]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain

[4]Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca, Salamanca, Spain

Correspondence to: López Anglada, Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer y Centro Regional de Hemodonación, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain. E-mail: lopez_anglada@gmail.com

Received: March 09, 2023; **Accepted**: March 25, 2023; **Published**: April 02, 2023

Citation: Anglada L, Bargay J, Jarque I, González A, Paiva B. Multiple Myeloma: Bortezomib, Lenalidomide, and Dexamethasone Intensol. J Clin Oncol Cancer Res . 2023;1(1):13-21

ABSTRACT

Background: The response to initial treatment in multiple myeloma (MM) plays a crucial role in determining the disease outcome. The triplet regimen - bortezomib, lenalidomide, and Dexamethasone Intensol (VRd) - is a widely used induction therapy for newly diagnosed MM due to its positive impact on overall survival. However, recent studies have shown superior responses and progression-free survival with the quadruplet regimen, daratumumab-VRd, albeit with increased toxicities. Balancing efficacy and toxicity in choosing an induction therapy is challenging, especially considering the advanced age and comorbidities in MM patients.

Objective: This study aims to identify biological markers that might influence the response rate to VRd therapy, offering valuable insights into optimizing treatment strategies.

Methods: In this cross-sectional study, MM patients treated with frontline VRd from January 2011 to May 2018 were analyzed. Various patient demographics, disease biology, disease burden, and stage at diagnosis were correlated with the response to VRd therapy after four cycles.

Results: Among 120 subjects analyzed, 50% achieved Very Good Partial Response (VGPR) or higher, 43% achieved Partial Response (PR), and 5% did not respond to treatment. Significantly different treatment

outcomes were observed between MM subtypes, particularly involving Ig, IgA, and Ig myeloma. Ig myeloma patients exhibited a higher incidence of VGPR or higher (79%) compared to Ig myeloma patients (37%) (P-Value < 0.0006).

Conclusion: The study concludes that Ig subtype myeloma is associated with a suboptimal response to frontline VRd therapy. These findings underscore the importance of considering MM subtypes when tailoring induction therapies for personalized patient care.

Keywords: Myeloma; Bortezomib; Lenalidomide; Dexamethasone Intensol; VRd.

ABBREVIATIONS

MM: Multiple Myeloma; VRd: Velcade Revlimid and dexamethasone; CR: Complete Remission; VGPR: Very Good Partial Response; PR: Partial Remission.

INTRODUCTION

Multiple Myeloma (MM) could be a heterogeneous incurable malady. whereas majorities of patients have indolent courses with sensible response to direct induction, some patients progress chop-chop despite treatment. No consistent correlation between the intensity of medical care and semi-permanent malady outcome presently exists [1]. Complete response has been incontestable to powerfully correlate with improved progression-free survival [2,3].

Despite distinctive multiple prognostic markers in myeloma, that embody neoplasm burden (stage), performance standing and tolerability to anti-myeloma medical care (fitness), the aggressiveness of malady (biology), and status of growth plasma cells to anti-myeloma agents (responsiveness) [4], there's no predictor-guided formula that may be utilized in choosing regimens to attain the simplest response.

Current normal initial medical care for patients with millimeter depends on the genetics risk of malady [5,6] and eligibility for autologous somatic cell Transplantation (ASCT) [7]. However, there's no general agreement on the quality induction program.

A three-drug program has been incontestable to be simpler as compared to jacket regimens. The addition of bortezomib to lenalidomide and Dexamethasone Intensol (VRd) as compared to lenalidomide and Dexamethasone Intensol (Rd) within the SWOG S0777 trial resulted in considerably improved Progression-Free Survival (PFS) and Overall Survival (OS) [8]. or so 525 patients were enclosed in section three multicenter study; they were indiscriminately allotted to VRd or lenalidomide and Dexamethasone Intensol (Rd) solely. VRd resulted in higher rates of overall response (82 versus seventy-two %) [8,9]. Moreover, VRd continues to represent associate applicable normal of care supported the longer-term follow-up knowledge [8].

Similarly, the chance of malady progression or death was considerably lower with daratumumab and lenalidomide and Dexamethasone Intensol than lenalidomide and Dexamethasone Intensol alone [10]. Herein, three-drug regimens ar the mainstay of initial medical care for millimetre whereas two-drug regimens should still be of importance in frail patients United Nations agency might not tolerate normal three-drug regimens [11].

Over the last twenty years, many new agents, like Immunomodulatory agents (IMiDs), Proteasome Inhibitors (PIs), being Antibodies (mAbs), are FDA-approved. These agents are incorporated into clinical tips and have remodeled our approach to the treatment of millimetre patients [12].

Additional frontline regimens for millimetre embody daratumumab, lenalidomide, Dexamethasone Intensol (DRd) [10], bortezomib, Cyclophosphamide, Dexamethasone Intensol (CyBorD) [13] and carfilzomib,

lenalidomide, Dexamethasone Intensol (KRd) [14]; have incontestable tolerability and effectuality with important improvement in overall response rates [9,10,13,14]. additionally, once scrutiny VRd to KRd at the Endurance E1A11 trial, it showed similar PFS and OS [14]. VRd remains to be the well-liked program given the potential overall survival profit and lower toxicity profile [8,9].

More recently, the advantage of adding a fourth drug is being evaluated in many clinical trials. The section two trial (GRIFFIN) irregular 207 patients to VRd with or while not daratumumab (D-VRd versus VRd). It showed that D-VRd resulted in a very higher overall response rate (99 versus ninety two percent) and deeper response (63% reached rigorous Complete Remission (sCR) and CR). However, toxicity was larger with D-VRd with higher rates of leucopenia and higher tract infections [15].

The association between depth of response and also the semi-permanent outcome remains a debated topic in millimetre, however, the connection between an entire response and progression-free survival has been additional consistent [16]. a major correlation between the action of Complete Response (CR) or excellent Partial Response (VGPR) and improved PFS, and so OS has been incontestable in eight out of 10 studies enclosed in a very meta-analysis [3].

Additionally, the action of response but a really sensible Partial Response (VGPR) once initial induction is associate adverse prognostic issue for Progression-Free Survival (PFS) in millimetre [2]. Therefore, achieving chromium or VGPR could be a valid surrogate marker of the treatment effectuality [2].

While debating between three-drug programs versus four-drug regimens about to win the deepest response to induction regimen for freshly diagnosed millimetre, equalization effectuality and toxicity could be a challenge because of advanced age and comorbidities related to the metastatic tumor population.

Biomarkers that may guide the choice of frontline medical care supported prediction for effectuality would be clinically helpful in determinative the simplest approach to attain highest profit in associate personal approach instead of a trial-and-error approach.

In this study, we tend to hypothesized that a selective subgroup of patients with freshly diagnosed millimetre, that share common biological markers, might not like frontline treatment with VRd.

MATERIAL AND METHODS

Based on previous studies demonstrating the simplest initial response to be powerfully related with survival outcomes [2,3,16], this study aims at evaluating the initial response rate to 3-6 cycles of frontline VRd as a surrogate marker for treatment effectuality. in addition, we tend to aimed to gauge whether or not malady burden, biology, or presenting clinical image impact response to VRd.

The primary outcome of this study was to spot if bound characteristics of metastatic tumor are related to higher or lower initial response rates to VRd. Results from our study could become a future platform in choosing associate induction program through a personalized approach.

This is a cross-sectional study as well as participants with freshly diagnosed millimetre. Participants were chosen from the cohort of patients with freshly diagnosed millimetre treated in our establishment from Gregorian calendar month 2011 till could 2018, and, followed for a minimum of the primary half dozen months once initiation of medical care.

We classified our cohort per response to medical care [17] into three groups: participants United Nations agency achieved a) Complete Response (CR) or excellent Partial Response (VGPR) b) Partial Response (PR) c) but partial response. To measure the result of malady burden, biology, and patients' fitness on the responsiveness to medical care, we tend to known many variables that might doubtless have an effect on

response to medical care and analyzed the correlation between completely different variables and response to medical care.

We classified our cohort supported gender, age at diagnosing, stage of malady [5], malady biology in terms of Free light-weight Chain analysis (FLC), and immunofixation (IgG, IgA, or immune serum globulin monoclonality). we tend to additionally classified our patients by their risk strata victimization light in place union (FISH) and genetics (standard versus high risk) [5].

Disease burden outlined because the p.c of bone marrow involvement with malignant plasma cells. CRAB criteria, symptom outlined as liquid body substance atomic number 20 >11 mg/dL, nephropathy outlined as liquid body substance creatinine >2 mg/dL, anemia outlined as hemoprotein level

For response assessment, we tend to use the International metastatic tumor social unit (IMWG) response definition [17]. For millimetre staging, we tend to use the International Staging System) [18]. Our Institutional Review Board (IRB) approved the analysis protocol.

Selection of Participants

This empiric study enclosed participants with freshly diagnosed millimetre United Nations agency were eighteen years or older and eligible for treatment with a bortezomib-based program (VRd or Vd) within the frontline setting. Participants had associate jap Cooperative medical specialty cluster (ECOG) 0-2 at the time of diagnosing, and no proof of organ dysfunctions unrelated to millimetre like viscus, hepatic, pulmonary, and/or central system disfunction.

We excluded patients United Nations agency had proof of different malignancies that needed active treatment.

VRd program followed the SWOG-S0777 study protocol [9] was given as 21-day cycle. Bortezomib was given at one.3 mg/m(2) intravenously on days one, 4, 8, and 11, combined with oral lenalidomide twenty five mg daily on days one-14 and oral Dexamethasone Intensol given as either (20 mg daily on days 1, 2, 4, 5, 8, 9, 11, and 12) or (40 mg weekly) [9]. All participants received 3-6 cycles of medical care. the quality protocol for indefinite quantity changes for toxicity was utilized [9].

STATISTICAL ANALYSIS

Data were analyzed victimization applied math Analysis software package (SAS) 7.4. Among the cohort of patients treated in our establishment at the chosen amount, we tend to enclosed in our analysis solely the patients United Nations agency received the bortezomib-based program, and also the cohort United Nations agency received VRd for a minimum of 3-6 cycles.

Data collected enclosed age at diagnosing, gender, presence of CRAB at the initial presentation, presence of extramedullary malady at the time of diagnosing, ISS stage, and p.c of bone marrow involvement at diagnosing, simple protein level at diagnosing, FLC restriction, FLC ratio, and risk classification for every participant.

We classified our cohort supported response standing into 3 teams (responders, partial responders, and non-responders). we tend to analyzed the correlation between every completely different variable and response standing. For categorical divided variables, we tend to used Chi-Square (Fisher's Exact) take a look at. For continuous variables, we tend to used supply multivariate analysis model.

A subgroup analysis was performed on the subgroup of patients United Nations agency showed a major distinction in response to medical care.

RESULTS

Starting Gregorian calendar month 2011 through could 2018, a hundred seventy-five patients were treated in our establishment for freshly diagnosed millimetre. 100 and twenty patients received bortezomib-based program, eightieth (96 subjects) received VRd and 2 hundredth (24 subjects) received Cupid's disease because of intolerance and fragility. All participants enclosed during this study were able to end 3-6 cycles of VRd.

The median age at diagnosing was sixty.5 (ranging from 39-73 years), sixty-two of participants were males and thirty eighth were females. cardinal p.c were lambda restricted and sixty-three were alphabetic character restricted. the bulk of our cohort had Ig or Ig monoclonality on immunofixation, thirty first were Ig and sixty-eight were Ig. forty first had > hour bone marrow involvement by malignant plasma cells. Response to medical care evaluated once the third cycle for all patients with five hundredth achieved VGPR or higher, forty fifth achieved PR, and 5 patients had malady progression (Table 1).

Immuno-globulin (Ig) Status	Response to Therapy after Cycle 3 Effective Sample size=93 Missing =3			Total
	CR or VGPR N %	Partial Response N %	Disease progression N %	
IgA	23 (79 %)	6 (21 %)	0	29 (31 %)
IgD	1 (100 %)	0	0	1 (1 %)
IgG	23 (37 %)	35 (56 %)	5 (8 %)	63 (68 %)
IgM	-	-	-	-
Total	47 (51 %)	41 (44 %)	5 (5 %)	93
Chi Square (Fisher's Exact) P-value				0.0006
*CR: Complete Response; *VGPR: Very Good Partial Response; *VRd: Bortezomib, lenalidomide and dexamethasone				

Table 1: Response Status by Immunoglobulin classification among VRd treated cohort.

Analysis of VRd Treated Cohort

We had ninety-six subjects World Health Organization received a minimum of three cycles of frontline VRd. xxxvi subjects had unsound sickness and forty-five had normal risk with missing risk strata on fifteen subjects. with reference to response assessment, five hundredth (48 of ninety-six subjects) were responders, forty fifth (43 of ninety-six subjects) were partial-responders and five-hitter were non-responders.

When analyzing response standing by gender in our VRd treated cohort, the ninety-six subjects were thirty-six females and sixty males. Despite having a numerically higher response rate in females with fifty-six responders, it absolutely was not statistically important (P-value zero.31). additionally, there was no statistically important distinction within the mean age at diagnosing among the 3 outcomes (P-value zero.114).

Analyzing sickness biology and its correlation with response to VRd, we tend to showed that neither FLC restriction (Kappa or lambda) nor the FLC quantitative relation (involved /uninvolved FLC) showed a statistically important distinction within the response to VRd (p-value zero.88 and 0.81 respectively). Molecular risk of sickness additionally did not show a distinction in response to VRd (p-value =0.52).

The risk stratification (high risk versus normal risk) between treatment outcomes additionally did not show a statistically important distinction P-value=0.52. However, once analyzing the sickness biology in terms of bodily fluid immunofixation results describing the human gamma globulin kind (monoclonal immune serum globulin, IgG, IgM, or IgD), we tend to showed clinically and statistically important distinction between responders,

partial-responders, and non-responders (P-value=0.0006). Remarkably, seventy-nine (23 of twenty-nine subjects) within the immune serum globulin cluster achieved VGPR or higher compared to thirty seventh (23 of sixty-three subjects) of the immunoglobulin cluster World Health Organization achieved VGPR or higher. the bulk of our partial-responders were within the immunoglobulin cluster, and every one 5 non-responders within the VRd cohort were immunoglobulin subtypes.

Sub Group Analysis

An unplanned subgroup analysis was performed on the immunoglobulin and immune serum globulin cluster to investigate the correlation between risk stratification and response outcomes in those subgroups. we tend to additionally analyzed the correlation between FLC restriction and also the presence of bone lesions at the time of diagnosing. we tend to designated to try and do subgroup analysis for those variables thanks to a discordance of prevalence within the study cohort, the bulk of our cohort had osteolytic bone lesions at diagnosing and regarding simple fraction had alphabetic character restriction.

Among subjects with immunoglobulin kind malignant tumor, neither risk of sickness (P-value= 1.52), FLC restriction (P-value= 2.0), nor presence of osteolytic bone lesions at diagnosing (P-value=0.51) correlate with treatment response. Additionally, within the immune serum globulin kind malignant tumor, our knowledge failed to show a statistically important distinction between risk strata, FLC restriction, or osteolytic lesions at diagnosing and treatment outcomes (P-values= one.0, 1.0, and 0.56 respectively). Other variables together with sickness burden, % of bone marrow involvement with malignant plasma cells, presence of CRAB criteria at diagnosing, presence of extramedullary sickness, and ISS stage did not show a statistically important correlation with treatment outcomes. Our results showed associate degree association between human gamma globulin monoclonality in millimeter and initial response to VRd. immunoglobulin kind malignant tumor showed to possess a less optimum response to frontline VRd, characterized by a better rate of partial response and a lower rate of VGPR or metal as compared to immune serum globulin malignant tumor patients.

DISCUSSION

Multiple myeloma is associate degree incurable sickness, achieving complete response is that the goal of medical aid because it correlates with improved overall survival and progression-free survival [2,3,16]. VRd is that the most popular frontline induction regime to this point thanks to its tolerability and its ability to induce a deep response in patients with new diagnosed millimeter no matter if followed by autologous vegetative cell transplantation or not. we tend to studied many factors which may have an effect on the initial response to VRd. we tend to summarized potential factors into patient demographics, sickness burden at diagnosing, sickness stage, and biology.

The main finding, we tend to report from this cross-sectional study is that sickness biology with reference to human gamma globulin monoclonality (heavy chain subtypes) encompasses a statistically important association with response outcomes. Although the impact of bodily fluid immunofixation was self-addressed in previous retrospective studies associate degreed failed to show an association with sickness outcomes, immune serum globulin malignant tumor was related to worse outcomes thanks to a better incidence of nephrosis. in a very giant multicenter retrospective study, that self-addressed identical question of the result of paraprotein on malignant tumor outcomes, no distinction was determined between immune serum globulin and immunoglobulin in overall survival. However, it showed a shorter PFS for immune serum globulin kind malignant tumor. This study all over that worse PFS was contributed to nephrosis and specifically higher levels of FLC excretion, that was a lot of outstanding within the immune serum globulin cluster. Their knowledge showed that patients with immunoglobulin or immune serum globulin subtype with identical level of urinary FLC excretion had identical incidence of kidney disease and poor survival.

We are news a distinct outcome, immunoglobulin paraprotein is related to suboptimal response to frontline victimization VRd, however showed no important distinction after we stratified subjects supported FLC kind in

our subgroup analysis.

Our study implicates that the human gamma globulin subtype of malignant tumor {could be|might be|can be|may we tend toll be} another issue that has to be taken into consideration as we choose a most popular regime for optimum response. Quadruplet regime with targeted being antibodies together with VRd as frontline medical aid in new diagnosed myeloma is superior to VRd in Overall Response Rate (ORR) and PFS, however, it should carry a better toxicity [15]. whether or not associate degree direct quadruplet regime would supply a much better response rate within the immunoglobulin subgroup as compared to triplet VRd isn't far-famed. whereas leveling edges and toxicities in choosing therapeutic regimens for patients with myeloma is crucial, any confirmation of our findings is important. A subgroup analysis victimization the previous study to investigate the result in immunoglobulin and immune serum globulin malignant tumor, victimization frontline D-VRd versus VRd, or a future giant randomized prospective study examination the response to D-VRd versus VRd supported human gamma globulin subtype of myeloma may facilitate validate our findings. Our knowledge may additionally probably have an effect on however we tend to stratify therapeutic regimens in numerous people, preferring quadruplet regime to VRd with immunoglobulin kind millimeter, particularly if it's within the context of molecularly unsound sickness.

There are sure limitations to our study. the tiny sample size within the VRd- treated cohort limits our conclusion; maybe a lot of cooperative effort with further establishments to extend our sample size would strengthen the validity of our results.

Designing the study as a cross-sectional retrospective study limits our results. though we tend to may judge the association between human gamma globulin monoclonality and treatment outcomes, we tend to are unable to state a causative relationship between immunoglobulin kind millimeter and poor response to frontline VRd.

We achieved the first aim of our study that is immunoglobulin subgroup of millimeter patients was related to lower response rates to frontline VRd. Our knowledge raises awareness of the importance of sickness characteristics and biology in treatment response. As we tend to aim at personalized drugs and planning individualized treatment algorithms in millimeter, future studies evaluating the effectiveness of varied treatment regimens for millimeter should incorporate sickness characteristics and biology collectively the vital parameters within the analysis.

CONCLUSION

We conclude that immunoglobulin kind millimeter was related to suboptimal response to frontline VRd. Our restricted single institutional study suggests that human gamma globulin monoclonality {could be|might be|can be|may we tend toll be} a very important parameter to be thought of as we stratify therapeutic regimens in myeloma. any studies would facilitate make sure our finding. millimeter remains associate degree incurable sickness and a sickness that happens in older people World Health Organization normally carry underlying comorbidities, having the ability to balance treatment-related edges and risks is crucial. Our findings {could be|might be|can be|may we tend toll be} vital as we aim towards personalized drugs.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTERESTS

None.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-2128.

2. Roberts K, Colquhoun S, Steer A, Reményi B, Carapetis J. Screening for rheumatic heart disease: current approaches and controversies. Nat Rev Cardiol. 2013;10(1):49-58.

3. BLAND EF, DUCKETT JONES T. Rheumatic fever and rheumatic heart disease; a twenty year report on 1000 patients followed since childhood. Circulation. 1951 Dec;4(6):836-843.

4. Tompkins DG, Boxerbaum B, Liebman J. Long-term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. Circulation. 1972;45(3):543-551.

5. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685-694.

6. Oli K, Porteous J. Prevalence of rheumatic heart disease among school children in Addis Ababa. East Afr Med J. 1999;76(11):601-605.

7. Oli K, Tekle-Haimanot R, Forsgren L, Ekstedt J. Rheumatic heart disease prevalence among schoolchildren of an Ethiopian rural town. Cardiology. 1992;80(2):152-155.

8. Martin DR, Voss LM, Walker SJ, Lennon D. Acute rheumatic fever in Auckland, New Zealand: spectrum of associated group A streptococci different from expected. Pediatr Infect Dis J. 1994;13(4):264-269.

9. Shet A, Kaplan EL. Clinical use and interpretation of group A streptococcal antibody tests: a practical approach for the pediatrician or primary care physician. Pediatr Infect Dis J. 2002;21(5):420-426; quiz 427-430.

10. Klein GC, Baker CN, Jones WL. Upper Limits of Normal" Antistreptolysin O and Antideoxyribonuclease B Titers. Appl Microbiol. 1971; 21(6): 999–1001.

11. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009;119(11):1541-1551.

12. Danchin MH, Carlin JB, Devenish W, Nolan TM, Carapetis JR. New normal ranges of antistreptolysin O and antideoxyribonuclease B titres for Australian children. J Paediatr Child Health. 2005;41(11):583-586.

13. Kim S, Lee NY. Asymptomatic infection by Streptococcus pyogenes in schoolchildren and diagnostic usefulness of antideoxyribonuclease B. J Korean Med Sci. 2005;20(6):938-940.

14. Steer AC, Vidmar S, Ritika R, Kado J, Batzloff M, Jenney AW, et al. Normal ranges of streptococcal antibody titers are similar whether streptococci are endemic to the setting or not. Clin Vaccine Immunol. 2009;16(2):172-175.

15. Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. Pediatrics. 1998;101(1 Pt 1):86-88.

16. Mhalu FS, Matre R. Antistreptolysin O and antideoxyribonuclease B titres in blood donors and in patients

with features of nonsuppurative sequelae of group A streptococcus infection in Tanzania. East Afr Med J. 1995;72(1):33-36.

17. Nimmo GR, Tinniswood RD, Nuttall N, Baker GM, McDonald B. Group A streptococcal infection in an aboriginal community. Med J Aust. 1992;157(8):521-522.

18. Sethi S, Kaushik K, Mohandas K, Sengupta C, Singh S, Sharma M. Anti-streptolysin O titers in normal healthy children of 5-15 years. Indian Pediatr. 2003;40(11):1068-1071.