



NIRMALA COLLEGE OF PHARMACY MUVATTUPUZHA



NATIONAL CONFERENCE

Nano-based Drug Delivery Systems; Recent Developments and Future Prospects

7 OCTOBER 2023

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**JOURNAL OF INNOVATIONS IN
APPLIED PHARMACEUTICAL SCIENCES**



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National Conference on Nano-based Drug Delivery Systems; Recent Developments and Future Prospects conducted By Nirmala College of Pharmacy, Muvattupuzha, in association with Indian Pharmaceutical Association on 7 October 2023

RESEARCH ARTICLE(S)

ASSESSMENT OF PHYSICAL FUNCTIONING IN RHEUMATOID ARTHRITIS PATIENTS AFTER RITUXIMAB THERAPY USING HEALTH ASSESSMENT QUESTIONNAIRE-DISABILITY INDEX

ANNA MARIA JOY , AKSHARA SHAJI , SHANIYA MATHEW , DR.SUJA ABRAHAM Pages 1-4

[VIEW PDF](#)

TOXICITY PROFILE OF CHEMOTHERAPY REGIMENS FOR MULTIPLE MYELOMA PATIENTS USING CTCAE CRITERIA

ANTONY V R, ARPITH ANTONY, HELAN KURIAN, JEEVA ANN JIJU, TIMY THOMAS, JITHIN SUNNY, SUJA ABRAHAM Pages 5-7

[VIEW PDF](#)

ISOLATION OF EMBELIN FROM EMBELIARIBES BERRIES FOR THE DEVELOPMENT OF TOPICAL ANTI-INFLAMMATORY PREPARATION

DR. R. BADMANABAN, MARIA S.PADATHIL , HANNA PARVEEN, DONA MERIN JOY, SHAHANA MAJEED, JOYCYMOLS, DR. DHRUBO JYOTI SEN Pages 8-18

[VIEW PDF](#)

DESIGN AND CHARACTERISATION OF TOPICAL EMULGEL CONTAINING NEEM OIL FOR ITS ANTIDANDRUFF PROPERTIES

EBY GEORGE, DR DHANISH JOSEPH, ABITHA N JABBAR, KHANSA BEEGAM M A, NIMISHA JOSEPH, MAHIMA FRANCIS, ANJU BOBAN, ANN MARIA ALEX Pages 19-23

[VIEW PDF](#)

DEVELOPMENT OF IMPLANTABLE DRUG DELIVERY SYSTEM OF EMBELIN FOR THE TREATMENT OF BREAST CANCER

RINCY. K. K, DR. DHANISH JOSEPH, BINSHA URUMEEES, ANN MARIYA JOSE, ATHIRA ANILAN Pages 24-28

[VIEW PDF](#)

COMPARATIVE INSILICO DOCKING STUDY INVOLVING ANTAGONISTIC ACTIVITY OF COUMARINDERIVATIVES ON EGFR AND CDK2

RIYA ANN THOMAS, EVA SARA SUNIL, ANNA ABEL FERNANDEZ, SOORYA ANIL, ANJANA ANTONY, ANN MARIA DAVIS, GODWIN THOMAS, SARANYA T S, GREESHMA SREERAM, DR. ELIZABETH ABRAHAM P Pages 29-35

[VIEW PDF](#)

ASSESSMENT OF PATIENT KNOWLEDGE, PRACTICE AND ADVERSE EVENTS OF INSULIN ADMINISTRATION AND STORAGE TECHNIQUES IN PATIENTS WITH DIABETES

ANTRIYA ANNIE TOM, NAMITHA ANTONY, PAVITHRA ASHOK, MUHAMMAD ABDUL KHADIR PS, JUHY JOJO Pages 42-46

[VIEW PDF](#)

FORMULATION AND EVALUATION OF HERBAL AFTERSHAVE GEL

CELU MARIYA FRANCIS, RIYA GEORGE, ANASWARA SANKAR, ANCI I J, MANJU MARIA MATHEWS, BADMANABAN R Pages 47-50

[VIEW PDF](#)

EVALUATION OF ANTIMICROBIAL ACTIVITY OF A HERBAL MIXTURE

DEEPA JOSE , SINI BABY, SUJJALA SUBASH, GIFTY LAWRENCE, ANEESA ANOOB , LINTA JOSE Pages 59-63

[VIEW PDF](#)

ONLINE SUBMISSION



Online ISSN:2455-5177

CODEN (CAS-USA): JIAPAW

Impact Factor: 5.832

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KEYWORDS



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1.0

2.0

3.0

INFORMATION

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EFFICIENT MICROWAVE SYNTHESIS OF COUMARIN DERIVATIVES WITH EVALUATION OF THEIR ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES

ANZIYA P A, SARANYA T S, ANJALI K, ANJALI KRISHNA, SINI BABY, DIVINE P DANIEL

Pages 124-130

[VIEW PDF](#)

COSMETIC USE RELATED ADVERSE EVENTS AND NEED FOR COSMETOVIGILANCE

MERRIN JOSEPH, KARISHMA SHAJI, MAHIN T M, NANDANA P B, KRISHNA DAS

Pages 64-71

[VIEW PDF](#)

A RETROSPECTIVE STUDY OF CLINICAL PROFILE OF VIPER BITE CASES IN SELECTED HOSPITALS IN CENTRAL KERALA

ANUMOL SAJU, ANTRIYA ANNIE TOM, ABY PAUL, SWAPNA SAJU, DONA JOHNSON, JESYLN JOE THOMAS, KUTTIKADEN PAGES 72-74
JOY STEFFI, JOYAL M JOLL

[VIEW PDF](#)

FORMULATION AND EVALUATION OF HERBAL TOOTHPASTE CONTAINING EUPATORIUM TRIPLINERVISLEAF EXTRACT

VIDYA PETER, ROSNA BABU , SHERRY SEBASTIAN, ANGEL JAEMON, ANGEL JAEMON, ANAGHA V T, JEEVAN SAJEEV

Pages 36-41

[VIEW PDF](#)

IN VITRO SCREENING OF ICACINACEOUS PLANTS INDIGENOUS TO KERALA

DR.ELIZABETH ABRAHAM P, FRINTO FRANCIS, PRADEEP R NAIR, ATHUL RAJ, RAJI RAJAN, ANAMIKA K. NAIR,
PROF.DR.BADMANABAN.R

Pages 51-58

[VIEW PDF](#)

FORMULATION AND EVALUATION OF BUCCAL FILM OF AN ANTIHYPERTENSIVE DRUG

ASHINAA BENEDICT, IRIN ROSE PAUL, DR. MANJU MARIA MATHEWS, DR. BADMANABAN R

Pages 75-80

[VIEW PDF](#)

A PROSPECTIVE SURVEY TO ASCERTAIN THE SYMPTOMS, HEALTH ISSUES AND SUBSEQUENT OTC MEDICATION USAGE DURING MENSTRUATION AMONG COLLEGE STUDENTS

MINTU GEORGE, ANAGHA MELBIN, MARY PAUL DOMINIC, RESHMA DOMINIC, AYSHA SAJA P.S, JOBIN KUNJUMON
VILAPURATHU

Pages 81-84

[VIEW PDF](#)

A CROSS SECTIONAL STUDY TO ANALYSE THE ADR REPORTED IN A HOSPITAL DURING THE PAST THREE YEARS

SANGEETHA SUKUMARAN, VARSHA ELIZABETH JOBY, AMALA JOSEPH, APARNA JESTIN, JITHIN N P, SUMAYYA B
MUHAMMED, SUNU SEBASTIAN, JOBIN KUNJUMON VILAPURATHU

Pages 85-89

[VIEW PDF](#)

FORMULATION AND EVALUATION OF PREUNGUAL DELIVERY SYSTEM CONTAINING EUGENOL FOR THE TREATMENT OF ONYCHOMYCOSIS

MINI ELIAS, FLOWERLET MATHEW, GOURISREE T, ANILA RAJAN, ASHLY DAVIS

Pages 90-94

[VIEW PDF](#)

FORMULATION AND EVALUATION OF FLOATING CONTROLLED DRUG DELIVERY OF ANTI-ULCER DRUG LOADED MICROBALLOONS

BINDUMOL K C, FLOWERLET MATHEW, SHALOM SUNIL, ANGEL JOSE

Pages 95-100

[VIEW PDF](#)

PREPARATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM (FDSD) CONTAINING AN ANTIVIRAL DRUG

TEENA MOHAN, MARIYA SUNNY, MANJU MARIA MATHEWS, BADMANABAN R

Pages 105-109

[VIEW PDF](#)

FORMULATION AND EVALUATION OF CONTROLLED POROSITY ORAL OSMOTIC PUMP TABLETS OF FUROSEMIDE

TEENA CHACKOCHEN THEKKAL, REBA RENJU, MANJU MARIA MATHEWS, BADMANABAN R

Pages 110-113

[VIEW PDF](#)

FORMULATION AND EVALUATION OF TOPICAL GELS INCORPORATED WITH SOLID DISPERSIONS OF AN ANTIINFLAMMATORY DRUG

SETHU LEKSHMI, THERASE JOSE, MANJU MARIA MATHEWS, BADMANABAN R


Pages 114-119

[VIEW PDF](#)

IN VITRO ANTI-BACTERIAL SCREENING OF DRYNARIYA QUERCIFOLIA

ASHNA T, LINS MARY JOY, SIYARA ANTONY, SINDU T J, SHEEBA MOL P, SHUJI T S, SOUMYA K GEORGE

Pages 120-123


 [VIEW PDF](#)

CASE REPORT(S)

GUILLAIN-BARRE SYNDROME: A PAEDIATRIC CASE SCENARIO IN A TERTIARY CARE HOSPITAL AT SOUTHERN INDIA

NEVIN JOSEPH, ALFIN BABY, ELDHOSE ELIAS GEORGE, GOPIKRISHNAN T.S, MERRIN JOSEPH

Pages 101-104

 [VIEW PDF](#)

[Announcements](#) || [Editorial Board](#) || [Indexing](#) || [Contact](#)

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Journal of Innovations in Applied Pharmaceutical Science [JIAPS]

Content available at: www.saap.org.in ISSN: 2455-5177



ASSESSMENT OF PHYSICAL FUNCTIONING IN RHEUMATOID ARTHRITIS PATIENTS AFTER RITUXIMAB THERAPY USING HEALTH ASSESSMENT QUESTIONNAIRE-DISABILITY INDEX

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Article History	Abstract
<p>Received: 07-10-2023 Revised: 25-10-2023 Accepted: 10-10-2023</p> <p>Keywords: Rheumatoid arthritis, Rituximab, ACR, health assessment questionnaire-disability index (HAQ-DI), physical limitation, functional disability.</p>	<p>The most frequently used instrument for measuring self-reported physical function in rheumatoid arthritis is health assessment questionnaire – disability index. The objective of this study was to assess the effects of treatment with rituximab on patient-reported outcomes in severe rheumatoid arthritis patients. Rituximab was initiated in RA diagnosed patients who experienced treatment failure or decreased response on administration of conventional disease modifying anti rheumatic drugs. Treatment response after 1g of rituximab infusion was assessed at <6 months and >6months follow up period using patient reported outcome measure tools and laboratory investigations. Functional ability was evaluated using questionnaire and overall disability index was calculated. It was found that all patients achieved minimum clinically important difference (>0.2) from baseline HAQ value within 6 months of rituximab. Assessment of the functional ability demonstrated that majority of the patients experienced significant improvement in all domains of HAQ-DI after rituximab administration. Patient global assessment shared moderate correlation with almost all domains of HAQ-DI. Physical function as measured by HAQ-DI showed clinically meaningful improvement within 1 year of rituximab therapy. It has proven to be a safer and more effective treatment option when compared to conventional disease modifying antirheumatic drugs and has also helped in achieving better responses at a faster pace.</p>



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<https://doi.org/10.37022/jiaps.v8i3-S.505>

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology which is associated with progressive joint destruction, significant disability and long-term reductions in quality of life together with substantial social and economic costs [1]. Rheumatoid arthritis (RA) is an autoimmune disease affecting an estimated 0.4% to 1.3% of the world's population [2].

A multifaceted approach is required for successful management of RA due to the chronic nature and complexity of RA. A notable proportion of patients still do not achieve considerable clinical response despite the use of conventional Disease modifying anti rheumatic drugs (DMARDs) and anti-TNF agents as monotherapy or combination therapy. This led to introduction of a number of non-TNF biological agents in RA treatment.

Rituximab, a therapeutic agent that works by selectively depleting anti-CD20 –positive B cells, which has shown significant efficacy in modifying RA disease symptoms [3], is approved for treatment of moderately to severely active RA in patients with inadequate response to anti-TNF therapies [4]. Rituximab binding to CD20 depletes peripheral B cells through cell-mediated and complement dependent cytotoxicity and promotion of cell apoptosis [5 –8].

Disability measured by self-reported questionnaires is one of the main outcome measures in clinical trials and observational studies in RA [9]. The most frequently reported Patient reported outcome measures (PROMs) instrument that is considered the gold standard for assessing functional limitations in RA is the HAQ DI questionnaire.

The HAQ analyses the capacity to perform different activities of daily living [10] and is a valid, accepted tool for measuring disability in RA [11, 12].

This study aims to evaluate the effects of rituximab therapy on rheumatoid arthritis patients using patient-reported outcome measure, HAQ-DI.

Patients and Methods

Fifty five adult patients, both male and female (aged ≥18 yr) who were diagnosed with RA according to ACR criteria and

experienced decreased treatment response with conventional DMARDs were included in the study. All were out-patients visiting the rheumatology department of a tertiary care hospital between October 2022 - May 2023. Patients unwilling to participate, patients being treated for cancer and those with missing and incomplete data were excluded. The study protocol was approved by the Institutional Ethics Committee of the tertiary care hospital. Prior to the commencement of the study, all participants were made familiar with the research process and were requested to sign an informed consent form. Data collected through individual patient interviews and from medical records were recorded in a structured proforma at baseline, <6 months and >6 months of therapy. Demographic data of RA patients including age, gender, BMI, family history, comorbidities and duration of disease were recorded. Physical and clinical findings, including the number of tender joints (TJC), number of swollen joint (SJC), physician global assessment (PGA), ESR, CRP and RF were recorded by the consultant rheumatologist. Treatment effects after intravenous administration of 1g rituximab were assessed using validated PRO instruments such as i) Pain score measured with a 10cm visual analogue scale (VAS) ii) Physical functioning and disability was assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) iii) Patient Global Assessment (PtGA) of Disease Activity recorded using 10cm VAS scale.

The HAQ-DI includes items that assess fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both the upper and lower extremities. There are 20 items in eight categories that represent a comprehensive set of functional activities - dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each category contains at least two specific sub-category questions. For each item, there is a four-level response set that is scored from 0 to 3, with higher scores indicating more disability (0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; and 3 = unable to do) [13].

To calculate the HAQ-DI, the highest sub-category score determines the value for each category, unless aids or devices are used. The category scores are then averaged into an overall HAQ-DI from zero to three. Scores of 0 to 1 generally represent mild to moderate difficulty, 1 to 2 represent moderate to severe disability, and 2 to 3 indicate severe to very severe disability. The use of aids or devices or physical assistance increases a score of zero or one to a two to more accurately represent underlying disability; scores at a 3 are not modified [13].

Results

The baseline demographic and clinical characteristics of the RA patients were summarised, with count and percentages for the categorical variables & mean ± standard deviation (SD) for numerical variables. Patients were split into 3 groups according to duration after rituximab therapy: Baseline,<6 months,>6 months. The outcome measure chosen was improvement in functional disability in different domains of HAQ. Statistical analyses were performed using IBM SPSS,Version 28 (SPSS Inc., Chicago, IL, USA). Statistical significance was set as a p value of 0.05 or less. Correlations were determined using Spearman Correlation method.

Statistical comparisons using one way ANOVA were done to test the significant effects of treatment. A total of 55 eligible patients were enrolled. As per patient demographic data portrayed in Table.1, female patients outnumbered males (females =85.71% , males =14.28%). At inclusion, the mean age was 53.65 ± 15.42 years and mean disease duration was 7.29 ± 4.93 years. There was a high prevalence of positive rheumatoid factor with a mean of 209.48 ± 230.81.The most prevalent comorbid condition found among RA patients is hypothyroidism(34%) followed by diabetes mellitus(27%) and interstitial lung disease(13%).Only a small proportion of patients (18%) had a family history of rheumatoid arthritis.

Table 1.PATIENT DEMOGRAPHICS

PATIENT DEMOGRAPHIC (N = 45)		N (%)	MEAN ± SD
Age			53.65 ± 15.42 years
Gender	FEMALE	48 (85.71)	
	MALE	8 (14.28)	
BMI			25.87 ± 3.95
Co morbidities	Interstitial Lung disease	7 (12.5)	
	Diabetes mellitus	15 (26.78)	
	HYPOTHYROIDISM	19 (33.92)	
Family History		10 (17.85)	
Rheumatoid factor (RF)			209.48 ± 230.81
Disease duration			7.29 ± 4.93 years

Comparing the data after treatment from baseline, PtGA dropped from 5.81±1.17 to 2±0.92 after 6 months of therapy. Patient reported pain score decreased from 6.76 ±0.89 to 5±0.74 (p=0.050 within 6 months of therapy and to 4.45±0.97 (p=0.001) after 6 months of therapy. During the study, the mean HAQ-DI improved significantly, from 1.59 ± 0.31 to 0.77 ± 0.23 (p=0.383) within 6 months and to 0.75 ± 0.23 after 6 months after introduction of rituximab. (Table 3).

Table 3.IMPROVEMENT IN Patient reported outcome measures

MEASURE	BASELINE (MEAN ±SD)	<6 MONTHS (MEAN ± SD)	p-value	>6 MONTHS (MEAN ±STD)	p-value
PATIENT GLOBAL ASSESSMENT (PtGA)	5.81 ±1.17	1.88 ± 0.87	0.176	2 ± 0.92	0.006
HAQ-DI	1.59 ± 0.31	0.77± 0.23	0.383	0.75 ± 0.23	0.000
PAIN	6.76 ± 0.89	5 ± 0.74	0.050	4.45 ± 0.97	0.001

All patients achieved an improvement of greater than 0.2 from baseline HAQ value within 6 months of rituximab, ie. the minimum clinically important difference (MCID).

Assessment of the functional ability demonstrated that majority of the patients reported “with much difficulty” for almost all the domains before rituximab, with highest score in the ‘walking’ domain which some patients were even ‘unable to do’(Fig 1).

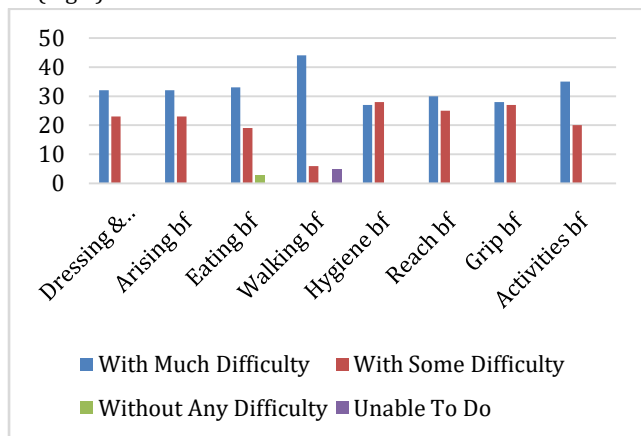


Fig 1. Functional Ability in Each Domain before Rituximab As Measured By HAQ-DI.

After treatment a good proportion of patients were able to carry out the day to day activities pertaining to all other domains 'without any difficulty' except for hygiene. A small proportion still experienced 'much difficulty' in domains of reach, grip, walking and activities. All patients had 'some difficulty' while performing hygiene related tasks (Fig 2).

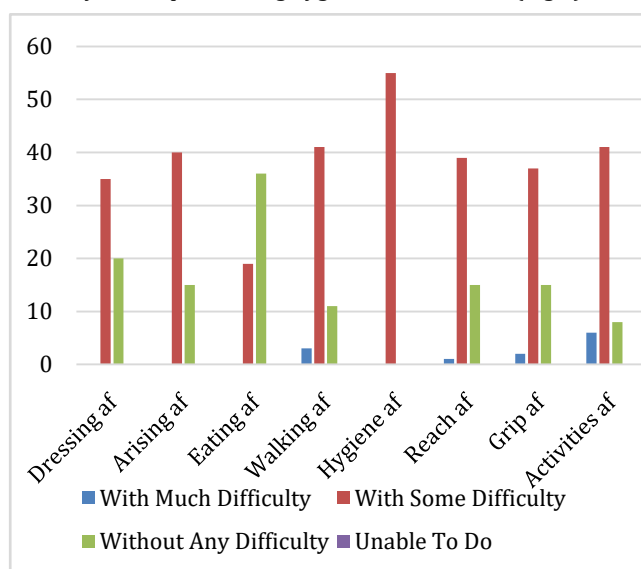


Fig 2. Functional Ability in Each Domain after Rituximab As Measured BY HAQ-DI.

Discussion

Patients in this observational study had active and longstanding disease despite the use of conventional DMARDs and had few remaining options for treatment. HAQ score was chosen as the outcome of interest as it is a patient-centered, clinically-relevant validated score that correlates highly with disability and quality of life and is also a continuous outcome, which is more sensitive to detect change than the traditionally used binary ACR20/50/70 score [14].

Prevalence of the HAQ-DI deterioration was 28-29%, and the HAQ-DI increased by 0.01 per year [15]. Yearly HAQ disability progression rates were higher in patients with mild to inactive RA than in those with moderate to severe RA, and patients with HAQ disability progression were characterised by low HAQ scores at baseline. Accordingly, RA patients with higher disease activity already had functional impairment and a lower possibility of HAQ disability progression [16].

Increases in all eight sub dimensions of the HAQ could be explained by pain, suggesting that in part the HAQ measures similar disability constructs to those assessed by the pain scale [17].

The level of improvement in Patient reported outcome is consistent with a previous study of rituximab, in which a statistically significant reduction in fatigue and improvement in physical (mainly bodily pain) and mental health scores was reported by rituximab patients compared with placebo patients [18]. Similar results were observed in our study, in whom the most significant reduction in disability was observed within 12 months after the introduction of rituximab.

Conclusion

In agreement with the results of the published clinical trials, our results indicated that RTX treatment is associated with improvement in joint swelling and tenderness coupled with significant drop in the levels of serum inflammatory markers in active RA patients refractory to multiple DMARDs. Rituximab was rated to be a much better treatment option than conventional ones by majority of the physicians and patients in this study.

Patient-reported physical function, measured by mean changes from baseline in HAQ-DI and the proportion of patients with clinically meaningful changes, confirmed the benefit of the therapy. These analyses indeed proves that rituximab treatment can produce rapid and sustained improvements over time, as demonstrated by higher ACR responses.

Conflict Of Interest

Nil

Author Contributions

Anna Maria Joy: Data curation & interpretation, manuscript drafting & editing Dr Suja Abraham: Study design, Methodology, draft revision Akshara Shaji & Shaniya Mathew: Data collection

Funding

This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit services.

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