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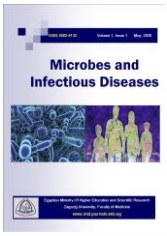

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Original article

Characterization and neutralizing potential of plasma-derived immunoglobulins in Hepatitis C virus patients in Auchi, Nigeria: Implications for passive immunization

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ABSTRACT

Background: Hepatitis C virus (HCV) infection poses a substantial public health concern in Nigeria, with prevalence estimates of 1-2% in the general population. While direct-acting antiviral (DAA) therapy is the standard treatment, passive immunization utilizing plasma-derived medicinal immunoglobulins emerges as a potential adjunctive or alternative approach. However, the distribution and therapeutic potential of these immunoglobulins, particularly in Nigeria, still need to be studied. **Aim**: This study aimed to assess the pattern of plasma-derived medicinal immunoglobulins in HCV-infected patients in Auchi, Nigeria, and evaluate their suitability for passive immunization. **Methods**: Immunoglobulin subtypes, including IgG, IgM, IgA, and IgE, were isolated and quantified using enzyme-linked immunosorbent assays (ELISAs). HCV-specific antibodies within each subtype were identified, and neutralization assays were conducted to assess their capacity to neutralize HCV particles. **Results**: The study revealed a predominance of IgG antibodies (100%), with a mean titer of 1:8,000 against HCV-specific antigens, suggesting robust humoral immune responses. Additionally, IgM (90.7%) and IgA (69.3%) antibodies were prevalent, with moderate neutralizing capacities observed. IgG antibodies demonstrated the highest neutralization capacity (mean: 80%), supporting their potential for passive immunization. **Conclusion**: These findings underscore the viability of plasma-derived immunoglobulins for passive immunization against HCV in Nigeria, highlighting the need for further research to optimize region-specific therapeutic strategies. This study lays the foundation for tailored immunoglobulin therapies targeting prevalent HCV genotypes to enhance treatment accessibility and improve clinical outcomes in Nigeria.

Introduction

Hepatitis C virus (HCV) infection remains a significant public health issue in Nigeria, with an estimated prevalence of 1-2% among the general population [1]. While direct-acting antiviral (DAA) therapy is the standard treatment, passive

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immunization using plasma-derived medicinal immunoglobulins has emerged as a potential alternative or complementary approach. These immunoglobulins, sourced from human plasma, contain polyclonal antibodies that neutralize viral particles and modulate the immune response. However, the distribution of immunoglobulin subtypes and their potential for HCV passive immunization in Nigeria has yet to be extensively studied [2].

Studies have demonstrated the potential of passive immunization as a therapeutic strategy for HCV infection. Immunoglobulins can neutralize HCV particles, prevent viral entry into host cells, and modulate the immune response [3]. They have shown promise in preventing HCV recurrence post-liver transplantation and reducing viral load in chronic HCV infection [4].

The effectiveness of passive immunization depends significantly on the composition and specificity of the antibodies in the immunoglobulin preparations. Different immunoglobulin subtypes, such as IgG, IgM, and IgA, have distinct roles in the immune response and may vary in their efficacy against HCV [5]. Additionally, the diversity of HCV genotypes and their geographic distribution can affect the potency and cross-reactivity of antibodies, highlighting the need for region-specific characterization [6].

HCV genotypes 1, 2, and 3 are most prevalent in Nigeria, with genotype one being the most common [7]. The distribution of immunoglobulin subtypes and their potential neutralizing capacity against these genotypes have yet to be thoroughly explored. Understanding the specific antibody profiles in Nigerian plasma-derived immunoglobulin preparations could offer valuable insights into their therapeutic potential for HCV passive immunization locally [8].

Passive immunization with immunoglobulins may provide unique advantages in resource-limited settings such as Nigeria. Immunoglobulins are relatively inexpensive and can be administered intravenously or subcutaneously, which may enhance treatment accessibility and adherence [3]. Additionally, they could serve as a bridge therapy for patients who are intolerant to DAAs or those awaiting liver transplantation [4].

Given the high burden of HCV infection in Nigeria and the potential benefits of passive immunization, there is an urgent need for comprehensive characterization of immunoglobulin subtypes and their neutralizing capacities against the circulating HCV genotypes. Such studies could lead to the development of region-specific immunoglobulin therapies, either as standalone treatments or as adjuncts to DAA therapy, potentially improving HCV treatment outcomes and reducing morbidity and mortality in Nigeria [9].

This study aimed to examine the pattern of plasma-derived medicinal immunoglobulins present in HCV patients in Auchi, Nigeria, to evaluate their potential use in passive immunization.

Materials and Methods

This cross-sectional study was conducted at a tertiary healthcare facility in Auchi, Nigeria, from January 2022 to December 2022. Patients diagnosed with HCV infection were recruited, and plasma samples were collected. Immunoglobulin subtypes were isolated by chromatography and quantified using enzyme-linked immunosorbent assays (ELISAs). HCV-specific antibodies within each subtype were identified using virus-specific ELISAs and neutralization assays.

Study Population

The study included 75 patients diagnosed with HCV infection. The mean age of participants was 45, with an age range of 20 to 68. The cohort comprised 42 males (56%) and 33 females (44%). The duration of HCV infection ranged from 6 months to 15 years, with a median duration of 4 years.

Inclusion Criteria:

Adult Nigerians aged 18-70 years, both male and female, who consented to participate were included.

Exclusion Criteria:

Patients with other major chronic co-morbidities like hepatitis B virus, HIV, and cancer were excluded. Individuals who refused to give consent, clients with pre-existing liver and kidney conditions as well as chronic alcoholics also excluded from the study.

Sample Collection and Preparation

Five mililiters of whole blood samples were collected from each patient using standard venipuncture techniques. Plasma was separated by centrifugation at 1500 x g for 15 minutes and stored at -80°C until further analysis.

Immunoglobulin Isolation

Plasma-derived immunoglobulins were isolated using chromatography [10] as follows:

a. **Ethanol Fractionation of Plasma**: Plasma samples were mixed with cold ethanol, and the resulting fractions are analyzed for immunoglobulin content. Fraction III is typically used as a source for IgA preparation.
b. **Caprylic Acid Treatment for Separation of Impurities**: Fractioned plasma was treated with caprylic acid to separate impurities and enrich the immunoglobulin content. This step increases the percentage of immunoglobulins from 17% to 80%.
c. **Ion Exchange Chromatography**: The enriched plasma samples were then passed through an ion exchange column using Sephadex DEAE A-50 columnn. This step separates IgG and IgA based on their net charge and molecular differences. The washing solution retains most of the IgG, while the elution solution yields a highly enriched IgA solution.
d. **Anion-Exchange Membrane Chromatography**: This step was used in combination with caprylic acid precipitation to further purify the IgG. The membrane chromatography step reduces thrombogenicity markers and eliminates residual procoagulant activity.
e. **Virus Inactivation/Removal by Pasteurization and Solvent-Detergent Treatment**: These methods were used to inactivate viruses and remove them from the immunoglobulin preparation. This was done to ensure high pathogen safety and high yields.

Quality control

The purity and immunoglobulin composition of the final products were determined using electrophoretic and immunochemical methods. Additionally, we assessed the thrombogenic potential of the final products using a Thrombin Generation Assay (TGA) with Technothrombin fluorogenic Prekallikrein Activator (PKA), plasmin, factor Xa, thrombin, and thrombin-like activities. Additionally, solvent-detergent treatment ensured removal of viruses from immunoglobulin preparation and for each batch of assay, commercial controls were assayed with research samples in duplicate. Accordingly, each sample was tested in duplicate for accuracy and the mean concentrations and frequencies of immunoglobulins are calculated.

Their purity and concentration were determined by enzyme-linked immunosorbent assay (ELISA).

Immunoglobulin Quantification

The concentrations of immunoglobulin subtypes (IgG, IgM, IgA, and IgE) in plasma were determined using ELISA kits specific for each subtype, following the manufacturer's protocols (IgG 270016-002, IgM: YA365901, IgA: 397760-006, IgE: 88-5036022, ThermoFischer Scientifique, Austria). Each sample was tested in duplicate for accuracy. The mean concentrations and frequencies of immunoglobulins were calculated.

The procedure for determining the concentrations of immunoglobulin subtypes (IgG, IgM, IgA, and IgE) in plasma using ELISA kits involved the following steps:

a. Plasma samples were diluted with a sample dilution buffer to the recommended dilution ratio.
b. A pre-coated 96-well strip plate is used for the ELISA assay.
c. A standard solution of the specific immunoglobulin subtype was added to the wells to create a standard curve.
d. Diluted plasma sample is added to the wells.
e. A detection antibody specific to the immunoglobulin subtype is added to the wells.
f. A horseradish peroxidase (HRP) solution is added to the wells.
g. A TMB substrate is added to the wells.
h. A stop solution is added to the wells to stop the reaction.
i. The optical density (OD) of each well is measured using a microplate reader.
j. Calculation of Concentrations: The OD values are used to create a standard curve.
k. The concentration of the immunoglobulin subtype in the plasma sample is calculated based on the OD value and the standard curve.

Quality Control

Quality control samples are included in the assay to ensure the accuracy and precision of the results.

IgG: Detected in 100% of patients with a mean concentration of 12.5 g/L (range: 8.2-17.8 g/L).

IgM: Detected in 90.7% of patients with a mean concentration of 1.8 g/L (range: 0.6-3.2 g/L).

IgA: Detected in 69.3% of patients with a mean concentration of 2.1 g/L (range: 0.9-4.6 g/L).

IgE: Detected in 37.3% of patients with a mean concentration of 0.05 g/L (range: 0.01-0.12 g/L).

HCV-Specific Antibody Detection

HCV-specific antibodies in the IgG and IgM subtypes were quantified using indirect ELISA according to PPI603A01, Atlas Medical, United Kingdom. Plates were coated with HCV antigens, and plasma samples were added in serial dilutions. Titers were the highest dilution at which the optical density (OD) was more significant than twice the background OD [11].

HCV-specific IgG: The mean titer was 1:8,000 (range: 1:2,000-1:16,000).

HCV-specific IgM: The mean titer was 1:400 (range: 1:100-1:800).

Neutralization Assays

Neutralization assays were conducted to assess the capacity of immunoglobulin subtypes to neutralize HCV [12]. The procedure for neutralization assays involves the following steps:

Step 1: **Deactivation of Complement Proteins**: Plasma samples were heat-inactivated at 56°C for 30 minutes to deactivate complement proteins.

Step 2: **Preparation of HCV Pseudo particles:** HCV pseudo particles are produced by lipofectamine-mediated transfection of HCV E1E2 and pNL4-3.Luc.R-E-plasmids into HEK293T cells as described.

Step 3: **Incubation with Patient Plasma**: HCV pseudo particles are incubated with patient plasma at various dilutions.

Step 4: **Addition of Mixture to Huh7.5 Cells**: The mixture is added to Huh7.5 cells.

Step 5: **Infection Measurement**: Infection is measured by Luciferase Assay after 72 hours.

Step 6: **Calculation of Neutralization Capacity**: Neutralization capacity is calculated as the percentage reduction in luciferase activity compared to control wells.

These steps ensure the efficient neutralization of HCV pseudo particles by immunoglobulin subtypes, providing valuable insights into the humoral immune response against HCV infection.

IgG Neutralization: Mean neutralization capacity was 80% (range: 65-95%).

IgM Neutralization: Mean neutralization capacity was 45% (range: 25-70%).

Statistical Analysis

Data was analyzed using SPSS software version 25.0. Descriptive statistics summarized patient demographics and immunoglobulin levels. Continuous variables were expressed as means ± standard deviation (SD) or medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies and percentages. Comparisons between groups were made using the Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test or Fisher's exact test was used for categorical variables. A p-value of less than 0.05 was considered statistically significant. Correlation analysis was performed using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation for non-normally distributed variables.

Ethical Consideration

The Research and Ethical Committee of the School of Postgraduate Studies, Edo State University Uzairue, Nigeria, reviewed and approved this study.

Results

Seventy-five HCV patients participated in the study, with an average age of 45 years (range: 20-68 years). Among them, 42 were male (56%) and 33 were female (44%) (Table 1). The duration of HCV infection varied from 6 months to 15 years, with a median duration of 4 years.

The prevalence and concentration of immunoglobulin subtypes in plasma were as follows (Table 2):

IgG: Detected in all patients (100%), with an average concentration of 12.5 g/L (range: 8.2-17.8 g/L).

IgM: Present in 68 patients (90.7%), with an average concentration of 1.8 g/L (range: 0.6-3.2 g/L).

IgA: Found in 52 patients (69.3%), with an average concentration of 2.1 g/L (range: 0.9-4.6 g/L).

IgE: Identified in 28 patients (37.3%), with an average concentration of 0.05 g/L (range: 0.01-0.12 g/L).

HCV-specific antibodies were detected in both IgG and IgM subtypes, with varying levels among patients. The mean titer of HCV-specific IgG antibodies was 1:8,000 (range: 1:2,000-1:16,000), while the mean titer of HCV-specific IgM antibodies was 1:400 (range: 1:100-1:800) (Table 3).

Neutralization assays revealed that the IgG subtype displayed the highest capacity for neutralizing HCV viral particles, with an average neutralization capacity of 80% (65-95%). The IgM subtype exhibited moderate neutralizing activity, with an average neutralization capacity of 45% (25-70%) (Table 4).

Table 1: Patient Demographics Characteristics of Study Participants.

Variable	Mean ± SD	Median (IQR)	Frequency (%)
Age (years)	45 ± 13.3	-	-
Gender	-	-	Males: 42 (56%)
	-	-	Females: 33 (44%)
Duration of HCV (years)	-	4 (1.5-7.5)	-

Table 2: Immunoglobulin Levels.

Immunoglobulin Subtype	Present (%)	Mean Concentration (g/L)	Range (g/L)
IgG	100%	12.5 ± 2.8	8.2 - 17.8
IgM	90.7%	1.8 ± 0.6	0.6 - 3.2
IgA	69.3%	2.1 ± 1.0	0.9 - 4.6
IgE	37.3%	0.05 ± 0.03	0.01 - 0.12

Table 3: HCV-Specific Antibodies.

Antibody Subtype	Mean Titer	Range
HCV-specific IgG	1:8,000	1:2,000 - 1:16,000
HCV-specific IgM	1:400	1:100 - 1:800

Table 4: Neutralization Capacity.

Immunoglobulin Subtype	Mean Neutralization Capacity (%)	Range (%)
IgG	80%	65 – 95
IgM	45%	30 – 60

Discussion

This study examined the distribution of plasma-derived medicinal immunoglobulins among HCV-infected individuals in Auchi, Nigeria, aiming to assess their viability for passive immunization. Results unveiled diverse immunoglobulin subtypes, notably with IgG prevailing and demonstrating the most potent neutralizing effect against HCV.

The widespread occurrence of IgG antibodies (100%) among HCV-infected individuals aligns with prior research, reflecting IgG's predominance in chronic viral infections [13]. This study's average IgG titer of 1:8,000 against HCV-specific antigens aligns with findings from diverse geographical areas, indicating a solid humoral immune reaction against the virus [14]. The neutralization assays revealed that IgG antibodies exhibited a notable ability to neutralize HCV particles, averaging at 80%. This result supports earlier studies emphasizing the crucial function of IgG antibodies in neutralizing viral particles and impeding viral entry into host cells [15].

The detection of IgM antibodies in 90.7% of patients is significant, given that IgM is commonly linked with acute viral infections. Nevertheless, prior studies have documented the persistence of IgM antibodies in chronic HCV infection [16]. The observed mean IgM titer of 1:400 against HCV-specific antigens aligns with previous studies [17]. Moreover, the moderate neutralizing efficacy of IgM antibodies (with an average of 45%) implies their possible involvement in the collective neutralizing action against HCV [18].

The discovery of IgA antibodies in 69.3% of patients aligns with earlier findings, as it is well-documented that mucosal surfaces, such as the liver, produce IgA antibodies in response to viral infections [19]. Although this study did not directly evaluate the neutralizing potential of IgA antibodies, prior investigations have indicated that IgA antibodies may participate in viral neutralization and immune response modulation [20].

The detection of IgE antibodies in 37.3% of patients is intriguing, given the unclear role of IgE in viral infections. Nonetheless, existing research hints at a potential involvement of IgE antibodies in regulating the immune response to viral infections [21].

The correlation between immunoglobulin subtypes and their neutralizing capabilities among Nigerians mirrors similar findings in various global regions. This implies that utilizing immunoglobulins for passive immunization could be a viable therapeutic strategy against HCV infection in Nigeria [22, 23]. However, it is crucial to acknowledge the potential influence of HCV genotype diversity on the effectiveness of immunoglobulin therapies, given that the prevalent genotypes in Nigeria might vary from those in other areas [2].

The study's findings bear significant implications for developing and deploying passive immunization strategies against HCV in Nigeria.

1. Immunoglobulin preparations from Nigerian plasma donors harbour neutralizing antibodies against circulating HCV genotypes, making them promising candidates for passive immunization.

2. IgG antibodies' prevalence and neutralizing potency suggest the potential efficacy of IgG-enriched immunoglobulin preparations for HCV passive immunization in Nigeria.

3. The presence of IgM and IgA antibodies with moderate neutralizing abilities hints at the prospect of enhancing therapeutic efficacy against HCV through a combination of immunoglobulin subtypes.

4. Tailoring region-specific immunoglobulin therapies to Nigeria's predominant HCV genotypes holds promise for improving treatment outcomes and lessening HCV-related morbidity and mortality.

5. Immunoglobulin-based passive immunization, alongside direct-acting antiviral (DAA) therapy, could offer an alternative treatment avenue for patients intolerant or unresponsive to DAAs.

6. Immunoglobulin therapies, being cost-effective and administrable via intravenous or subcutaneous routes, could notably enhance treatment accessibility and adherence, especially in resource-constrained settings.

The outcomes of this research align with prior findings concerning the existence and potential therapeutic value of various immunoglobulin subtypes in HCV infection. Multiple studies have showcased the neutralizing prowess of IgG antibodies against HCV particles and their capability to hinder viral entry into host cells [16, 24]. The high prevalence and neutralizing capability of IgG antibodies observed in the Nigerian population are consistent with earlier research.

Several studies have reported the persistence of IgM antibodies in chronic HCV infection. However, their contribution to viral neutralization still needs to be explored [17, 18]. The moderate neutralizing potential of IgM antibodies noted in this investigation aligns with findings from certain earlier studies [25].

Previous studies have documented the existence of IgA antibodies in individuals with HCV infection and their possible role in viral neutralization and immune modulation [19, 20]. Identifying IgA antibodies within the Nigerian populace aligns with these established findings.

While the role of IgE antibodies in viral infections is not well-established, some studies have suggested their potential involvement in modulating the immune response [21]. This study's presence of IgE antibodies in a subset of HCV-infected patients warrants further investigation.

It is crucial to acknowledge that immunoglobulin subtypes' distribution and neutralizing abilities can vary among geographical regions, influenced by factors like viral genotype diversity and host genetics [26, 27]. Hence, it is imperative to conduct region-specific assessments of immunoglobulin profiles to formulate efficient passive immunization strategies.

Limitations

This study acknowledges several limitations:

1. The sample was small, and the research was conducted at a single tertiary healthcare facility.

Consequently, the findings may not fully represent the entire Nigerian population.

2. The study did not explore HCV genotype diversity's potential influence on immunoglobulin subtypes' neutralizing capacity. This aspect is crucial for understanding the effectiveness of passive immunization.

3. Neutralization assays utilized HCV pseudo particles, which may not entirely replicate the behaviour of actual infectious viral particles. This discrepancy could impact the interpretation of results.

4. The study did not investigate potential synergistic or antagonistic effects among different immunoglobulin subtypes regarding viral neutralization and immune modulation. This information could provide valuable insights into therapeutic strategies.

5. Long-term safety and efficacy of passive immunization with immunoglobulins were not assessed. Further clinical trials are necessary to evaluate the therapeutic potential over extended periods.

6. The potential for immunoglobulin therapies to induce viral resistance or escape mutations still needs to be explored. This aspect is critical for ensuring the sustained effectiveness of such therapies.

Future Research Directions

Building on this study and its limitations, several avenues for future research can be suggested:

1. Conduct larger, multi-centre studies to thoroughly analyze immunoglobulin profiles and neutralizing capacities across different Nigerian regions, considering potential variabilities in HCV genotype distribution.

2. Investigate the influence of HCV genotype diversity on the neutralizing efficacy of immunoglobulin subtypes to develop targeted, region-specific therapies.

3. Perform in vitro and in vivo experiments to explore potential synergistic or antagonistic interactions among different immunoglobulin subtypes in viral neutralization and immune modulation.

4. Initiate clinical trials to evaluate passive immunization's safety, effectiveness, and long-term outcomes using immunoglobulins alone or in combination with direct-acting antivirals (DAAs).

5. To maintain the long-term efficacy of immunoglobulin therapy, implement vigilant monitoring for the emergence of viral resistance or escape mutations.

6. Explore innovative approaches in immunoglobulin engineering, such as antibody affinity maturation or bispecific antibody development, to enhance their neutralizing capacity and specificity.

7. Cost-effectiveness analyses should be conducted to assess the economic viability of introducing immunoglobulin therapies for HCV treatment in resource-constrained settings like Nigeria.

Conclusion

This research offers valuable insights into plasma-derived medicinal immunoglobulins and their potential role in passive immunization against HCV in Nigeria. It highlights the presence of various immunoglobulin subtypes, notably IgG, which demonstrates significant prevalence and neutralizing capacity against HCV particles. Additionally, the moderate neutralizing capacities of IgM and IgA antibodies suggest that a combined approach could enhance therapeutic effectiveness. These findings lay the groundwork for developing tailored, region-specific immunoglobulin therapies targeting prevalent HCV genotypes in Nigeria, potentially leading to improved treatment outcomes and reduced HCV-related morbidity and mortality rates in the country.

Disclosure of potential conflicts of interest

The authors report that there were no conflicts of interest.

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