Ovidius University of Constanţa

Doctoral Medical School

Medical Doctoral Field

PhD Thesis

Psychiatric Disorders Related to Interferon Therapy in Chronic Hepatitis

Resume

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Constanţa 2015

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Keywords: Psychiatric Disorders, C Hepatitis, Interferon, Ribavirin, Cytokine, Neurotoxicity, Pretreatment, Clinical Evaluation Scales

Chapter I

Introduction

Hepatic infections with type B and C viruses are primary illnesses with evident clinical signs and symptoms and bioumoral liver values variations. Hepatic cirrhosis and hepatic cancer are the final stages of viral infection outcome. The viral infection can be transmitted through parenteral or nonparenteral pathways. Almost all kinds of viral B and C hepatic infections can benefit upon interferon treatment augmented by combination with ribavirine. Decreased viremia levels are registered. Interferon treatment can lead to side effects like different types of psychiatric disorders. Although interferon treatment in hepatic viral infections is well tolerated. Sometimes psychiatric symptoms are part of the clinical picture, complicating the outcome. [Modabbernia et al., 2013].

Chapter II

Importance and Actuality of the Subject

Life time prevalence high values of hepatic viral B and C infections is well known as a very important problem of public health due to chronicity of these infections, due to the high costs needed for the treatment and invalidity. Patients' life quality and productivity decrease. Specific(interferon) or augmentative (interferon and ribavirine) treatment is also the best therapeutical solution [Malone et al., 2005].

Objectives

1. Establishing pertinent solutions for preventing psychiatric disorders as a result of viral infection or interferon treatment and maintaining psychiatric manifestations at a certain subclinic level through the following interventions:

– specific psychiatric "pre-treatment" (anxiolitic, antidepressant, combined - augmentative, antipsychotic) in association or not with psychotherapy before begining interferon therapy for infected patients with B or C hepatic virus at risk for developing psychiatric disorders;

– prescribing and following adaptive and personalized therapeutic scheme adapted for every situation occured in order to avoid interferon drop-out.

2. Establishing specific types of clinical situations more frequently met during practice and setting specific guidelines for these comorbidities, optimizing case management considering patient's needs and rights to benefit on the best possible therapy and maintaining in the same time an optimum balance between costs and benefits.

3. Particularization possibilities in similar reactivity and outcome situations establishing follow-up personalized intervention.

4. Establishing follow-up guidelines involving registering data periodically considering the extended duration and potential relapses of both disorders.

5. Establishing the optimum therapeutic attitude in conditions of concomitant or successive complications, relapses or ameliorations of both disorders.

6. Establishing specific strategies in cases of preterminal patient for both patient and family, making sure respecting autodetermination and dignity.

7. Cost-benefit balance in conditions of administrating both therapies, grossly evaluating direct costs resulting in medication needed, human resources, other material resources, material loses due to patients' inability to work and due to invalidity and pension payments.

8. Both diseases being part of National Health Programmes, a better communication between the two medical disciplines is useful through a liaison medical discipline focusing upon psychiatric disorders in patients infected with B or C hepatic viruses, treated with interferon, fulfilling modern management tasks.

Chapter III
B and C Viral Hepatitis
1 General Informations. Recent Data

Hepatic virus was firstly identified and isolated through direct and indirect methods in 1989. Viral hepatitis represent infectious primary diseases with clinical or subclinic symptoms, causing biological values modifications, being associated or not with infection's persistence.

Diagnosis of viral infection involve two aspects which may be concomitant: liver disease diagnosis through evidencing hepatic cell acute lesion and etiological diagnosis through immunological tests. The main diagnostic criteria are clinical.

3 C Hepatitis

C hepatitis virus is a monocatenar RNA virus with positive polarity containing 3011 aminoacids and 9400 nucleus particles, in size of 50-60 nm. The serological tests for C hepatitis are first generation ELISA tests and second generation ELISA 2. The RIBA tests identify antibodies against four proteins.

Epidemiology

C hepatitis is considered widely spread infectious disease. 50% of blood donors are infected. 10% to 50% of patient suffering of thalassemia have antibodies anti CHV(C hepatitis virus) [Alter et al., 1998].

C Chronic Hepatitis

C chronic hepatitis follows acute infection in 50% to 60% of cases, 20% are evolving to cirrhosis, 10% of cirrhotic patient being diagnosed with liver cell carcinoma [Alter et al., 1999].

Clinical Picture

Clinical features of the disease are insidious or asthenia is present. The progression is slow, every increase of serum transaminase level corresponding to a new episode of viremia. Chronic C hepatitis can be associated with immune diseases like type 2 mixed crioglobulinemia, both being responsive to interferon therapy.

Chapter IV

The Interferon

1 General Considerations

Natural Interferon

The three types of natural interferon are the following:

– α interferon synthesized in leucocytes;
– β interferon synthesized in leucocytes;
– γ interferon synthesized in T auxiliary lymfocytes.

3 Posology and Therapeutical Results

The α interferon has antiviral action inducing cell resistance to viral infections and modulation of immune system, viruses being neutralized or eliminating infected cells through anti proliferating action. Case management is personalised for patients suffering of previous infection severe psychiatric disorders (depressive disorder, bipolar mood disorder, psychosis) [Sockalingam et al., 2013]. The patient will receiveboth therapies: psychiatric chemo-therapy and interferon [Nelligan et al., 2008].

Interferon Treatment in C Chronic Hepatitis

C chronic hepatitis antiviral treatment is the solution for avoiding liver cirrhosis. A Roferon is administered in doses of 6 mil I.U. three times weekly subcutaneously or intra muscle for three months as initiation therapy. Normal transaminase levels request maintenance therapy with 3 mil I.U. three times weekly for another 3 months to an year with the same doses. Antiviral treatment for patients with chronic C hepatitis was improved by administering α pegylate interferon in association with ribavirine [Hadziannis et al., 2004]. Many patients with chronic C hepatitis 1b CHV and with high viral loading do not respond to the treatment, while discontinuing the treatment lead to further secondary complications [Carrat et al., 2004]. Weekly administration of subcutaneus α pegylate interferon is very convenient.

C hepatitis interferon treatment is completely effective in 46 % of cases, partial effective in other 25%. 25% of cases are nonresponsive [Vignau et al., 2005]. 50% of the responsive patients can relapse.

4 Cytokine Psycho - Neuro - Endocrinology

The term of "psycho - neuro - endocrinology" define structure and function interrelations between endocrine system and central nervous system and behavioral modulation as a result of interaction between the two systems. Extremly important role have peptidic neurotransmitters as corticotrophine releasing hormone and others [Kaplan & Sadock's, 2007].

5 Psychiatric Side Effects of Interferon Therapy

Among the unwanted cytokine side effects depressive symptoms can lead to a *depressive syndrome* in a large number of cases[Akiskal, 1981]. This concequent phenomenon to cytokine (IL1-α, IL1-ß) intake suggest a possible causality between citokyne therapy and possible occurance of major, severe and long lasting depressive episodes needing to be treated.

Neuropsychiatric side effects include somnolence, fatigue, lethargy, diziness, desorientation, attention deficit, irritability, emotional lability, social isolation, depression, anxiety, tention, fear, mania, sexual disfunctions, memory loss and cognitive impairement [Modabbernia et al., 2013].

Chapter V

Psychiatric Disorders Related to Interferon Therapy in Chronic Hepatitis

Interferon treatment administrated to B or C hepatitis viruses infected patient can cause unpleasant effects to the patients.

Common side effects caused by interferon treatment appear usually in the beginning of the cure, but also after a certain time; the most common are nausea, vomiting, asthenia, shivering, insomnia, irritability, weight loss, headache, mania, depression, anxiety, anorexia, psychosis. Sometimes is difficult to make the difference between a short time less intense side effect and a specific psychiatric disorder needing to be treated. Psychiatric disorder can cause temporarily or permanent interruption of interferon treatment in the condition of viral infection persistence, influencing the long term prognosis.**[Bandrabur Diana Lilia**, 2008].

Psychiatric disorders related to interferon therapy in chronic hepatitis are the following:

– anxious disorders;

– depressive disorders, including different degrees of depression intensity, psychotic symptoms or suicide;

– bipolar disorder I, II, III includind severe depressive episode, manic or mixed episodes;

– brief psychotic episode, schizophrenia-like or with prominent delusional features;

– dyskinezia;

– cognitive impairment.

2.1 Basal Immune Activation

Basal immune activation represent a risk factor and a depression inducer during interferon therapy [Wichers et al., 2006].

Finding depression in patients not receiving interferon treatment suggest that viral infection itself can cause depressive symptoms.

Depression Model as Immune System Dysfunction

Chronic stress triggers anxiety and depression onset through endocrine pathways and immune system.

3 Suicide

Suicide is the most important and severe complication of mood disorders, psychotic disorders, being defined as the voluntary action to take owns life by various means.

4 Bipolar Disorder

4.1 Etiopathogenics – Viral Component

Some theories consider the importance of viruses in schizophrenia and mood disorders' (bipolar disorder) etiology, widespread nervous central system's disorders. Viruses are incriminated because or

the neural tropism and latency in action. Some viruses alter dopamine's metabolism, while antipsychotic and antimanic drugs have antiviral action in vitro and in vivo [Yolken & Fuller Torrey, 1995].

4.2 Bipolar Depression

Bipolar depression is almost alike depressive disorder. Specific symptoms guide clinician to bipolarity. The importance of this matter was reflected in therapeutic choices and in evaluative prognosis [Akiskal, 2005].

4.3 Mania and Hipomania

Criteria for manic episode include a period of elated or irritable mood, persistent and abnormal, with at least week duration, three of the following symptoms being most prominent: exaggerated self-esteem, grandiosity, decreased need for sleep, psychomotor agitation, increased activity oriented on purpose, flight of ideas, distractibility, excessive hedonistic activities or risky behavior [Bandrabur et al., 2008 b].

Inflammation in Mood Disorders Outcome

Increased depression incidence was present in patients suffering of various inflammatory conditions, as: arthritis, psoriazis, diabetes, cancers, etc.

Serotonine, Stress and Depression

Abnormalities of serotonine levels are consudered the main mechanism of depression occurence. Sleep disorders, anorexia, diminished libido, anxiety and other symptoms are strong related to serotonine.Corticotrophin Releasing Hormone levels are influenced by serotonine in paraventricular hypotalamic nucleus resulting in stress axis modulations.

4.4 Mixed and Rapid Cycling Episodes

Mixed episodes include both manic and depressive characterisitcs.

Rapid mood swiches considered rapid cycling episodes can manifest as rapid variations of mood registered during one year period [Constant et al., 2005].

Rapid cycling bipolar disorder consists in four or more depressive, manic or mixed episodes in one year period. Rapid cycling bipolar disorder is more prone to register a chronic course than bipolar disorder with similar repeated episodes [Stahl, 2008].

5 Psychotic Episode

5.1 Unique Psychotic Episode

5.2 Repeated, Schizophreniform Psychotic Episode

Viral infection of the fetus during pregnancy can lead to psychotic disorders in adult life. Winter born babies are more frequently affected. the prevallenceof psychotic disorders is also higher in northern geographic areas. Schizophrenic patients have abnormal immune markers levels, including high interferon levels, decrease synthesis of 2-Interleukine (2-IL) and increased 2-Interleukine receptors' number. Spinal fluid levels of Immunoglobuline are high. The conclusion was schizophrenic patients express specific modification of the immune system [Roşoiu et al, 2009 b].

In the clinical practice complete expression of psychotic episode can be prevented through precociuos even pre-psychotic administration of specific antipsychotic medication in patients at high risk of psychosis [Roşoiu et al, 2009 c].

6 Persistant Delusional Disorder

Diagnostic criteria for delusional disorder include non-bizarre delusions, sometimes hallucinations can be present, mood variations are reduced in intensity and duration, functioning is relative preserved and is no substance involved. Considering the main subject of delusional ideas, there are: erotic delusion, grandiose delusion, jalousie delusion, persecution delusion, mixed and no specified [Kaplan & Sadock, 2001]. Specific clinical features can orientate clinician in chosing medication and establish outcome.

7 Cognitive Impairement

Blood high levels of 1 Interleukine and Tumor Necrosis Factor found in depressive patients are intense neurotoxic. Activated microglia and astrocytes release extra Oxygen and Nytrogene which have a toxic action upon neurons and oligodendroglias [Samargiu, Bandrabur et al, 2011a].

Tryptophan through kynurenine metabolite decreases two metabolic pathways activity.. Kynurenin - hidroxylaze splits kynurenine into 3 - hidroxy - antranilic acid and quinolinic acid. These metabolic products are neurotoxic and found at high levels in depressive patients and in Alzheimer disease (deteriorative, cognitive impairement) [Samargiu, Bandrabur et al, 2011b].

8 Diskinezia

Abnormal movements intensification because of psychiatric disorders treated with neuroleptic drugs was met also in α interferon treated patients for C hepatitis in persons with predisposition

9 Clinical Scales

9.1 Global Assesment of Functioning Scale (GAF)
9.2 Social and Occupational Functionning Assesment Scale – SOFAS
9.3 Global Assessment of Relational Functioning – GARF
9.4 Defensive Functioning Scale – DFS
9.5 Brief Psychiatric Rating Scale – BPRS
9.6 Hamilton Anxiety Rating Scale – HAM – A
9.7 Hamilton Depression Rating Scale – HAM – D
9.8 Scale for Assessment of Positive Symptoms – SAPS
9.9 Scale for Assessment of Negative Symptoms – SANS
9.10 Positive and Negative Symptoms Scale – PANSS
9.11 Lehman Quality of Life Interview – QOLI
9.12 Mini Mental State Examination – MMSE
9.13 Young Mania Rating Scale – YMRS
9.14 Montgomery – Asberg Depression Rating Scale
9.15 Zung Self – Rating Depression Scale

Chapter VI

The Treatment

1 Pharmacotherapy

1.1 Antidepressive Medication

Atipical antidepressants, selective serotonine re-uptake inhibitors (SSRI) are efficient drugs used in the treatment of depressive, obsessive-compulsive, anxious and other mood spectrum disorders symptoms In association with atipical antipsychotics, atipical antipsychotics are used in the treatment of psychotic disorders and major depressive disorders rezistant to usual medication [Asnis & De La Garza, 2005].

Antidepressant Effects Upon Immune Function Regulation

Recent research revealed decreased inflamation in depressive patients treated with antidepressants as a benefit of this [Stasi et al., 2013].

Inflammatory Hypothesis. Therapeutic Perspectives

Inflammatory processes are deeply involved in depression etiopathogenics. Yet antidepressant treatment decrease inflammatory concequences

1.2 Antimanic Medication, Mood Stabilizers

Antimanic therapy includes classical neuroleptic drugs (haloperidol), atipical second generation antipsychotics, long acting injectable antipsychotics, mood stabilizers as valproic acid and valproate, carbamazepine and clonazepam (rivotril) [Davis et al., 2005].

1.3 Antipsychotic Medication

Atypical or second generation antipsychotics, dopamine and serotonine inhibitors include following medication: risperidone, olanzapine, quetiapine, clozapine and ziprasidone.

2 Psychotherapy

Psychotherapy includes the interactions between the therapist and the person in therapy. Through the therapeutic method many aspects of life were brought into consciousness, helplessness is attenuated, adaptive coping skills are identified and a proper reaction to environment and its variations is promoted [Evon et al., 2013].

Chapter VII

C Hepatitis Treatment in Patients with Comorbid Severe Psychiatric Disorders

Recent estimation document that 20% of patients with severe psychiatric disorders are infected with C hepatic virus. Among these, 20% (4% of total number of patient with severe psychiatric disorders) will be treated also for cirrhosis and 3 % (0.6% among the total number of patients with severe psychiatric disorders) will be treated for liver adenocarcinoma [Kraus et al., 2003 a]. These patients will be also treated with interferon or interferon and ribavirine in some conditions and respecting some precautions. Concomitant or prior interferon antidepressive anxiolitic or antipsychotic treatment is an option for these cases [Kraus et al., 2003 b].

Chapter VIII

Research Methods in Psychiatry

1 General Research Methods

General research methods are statistic researches and therapeutic trials [Freeman & Tyrer, 2001].

Research means problem solving through sistematic actions in successive phases untill final result occures.

2 Specific Methods

Specific methods and epidemiology are part of biological psychiatry, evaluation scales for different psychiatric symptoms and disorders being used for quantifying and measurement.

Chapter IX

Psychiatric Disorders Pharmacology

Interaction between human body and medication generates two types of reaction. Pharmacokynetics means bodily action upon the drug and pharmacodynamics means medication's action upon the organism. Digestive absorbtion, circulatory distribution of the drug, metabolism and excretion are part of pharmacokynetic processes while pharmacodynamics quantifies medication effects upon cells.

Pharmacokynetics

Psychotropic drugs have action upon cortical neurons through arterial system. Oral medication is absorbed through digestion depending on lipid solubility, pH. Circulant medication has immediate effects. Intramuscle administration of the drugs induces a more rapid effect comparative to oral administration. Intravenous administration induces the fastest effect.

Drug Interactions

Some drug associations are supposed to be avoided or precautions are recommended. These interactions cause enzimatic inhibitions of P450 complex (CYP344). As a concequence tricyclic antidepressants, tetracyclics, SSRIs and antiaritmic drugs associatons are not recommended in clinical practice.

Chapiter X

Clinical Research. Material and Method

Present research is a retrospective analysis for patients diagnosed with chronic hepatitis treated with interferon since January 2007-December 2010 until July 2011, treated and followed up in Gastroenterology and Psychiatry Clinics of County Emergency Clinic Hospital of Constanta and ambulatory.

Inclusion criteria:

– signed informed consent;

– age between 18 and 80 years old;

– confirmed viral infection;

– explicit patient's acceptance of psychiatric preevaluation, specific and periodically testing and specific psychiatric medication.

Exclusion criteria:

– age under 18 or over 80 years old;

– patient's refusal to sign informed consent;

– patient's psychiatric preevaluation or periodical psychiatric testing refusal to accept;

– informed consent patient's withdrawal;

– pregnancy;

– serious illnesses.

Considering the 420 patients initially recruited, 370 among them accepted to participate in the research and signed the informed consent entering in the reseatch branches or in witness branches.

Patients were segregated in two branches:

RR 85 patients treated with IFNα2a (Roferon) and ribavirine (Copegus) compared with 85 patients in witness branch (RRM) (infected with C hepatic virus but without interferon treatment or those who stopped the treatment immediately after initiation)

PR 100 patients in treatment with Peg IFNα2a (Pegasys) and ribavirine (Copegus) compared with 100 patients in witness branch (PRM) (infected with C hepatic virus but without interferon treatment or those who stopped the treatment immediately after initiation)

Patients in witness branches of the study did not receive interferon treatment due to various reasons (refusal, signifficant adverse effects from the begining, lost to follow-up or left). Initial screening for C hepatitis and psychiatric disorders was performed for all patients. As a concequence they took part of research branches or witness branches after compulsory signing informed consent. Psychiatric evaluation included psychiatric interview throgh specific evaluation and autoevaluation

scales for different types of psychiatric pathology. this tests were performed at initiation and during periodical skeduled visits. Longitudinal psychopatological evaluation of the patients was performed. Study design included several visits; at each visit specific parameters were evaluated.

Visits were skeduled every thirty days for the first six months; after that visits were skeduled every ninety days. the final visit includes conclusion for each case. six months visits include also partial conclusions – tabel 10.1.

Interferon and ribavirine common subjective side effects were autoevaluated by each patient quoting intensity on 1 to 10 digits side effects intensity scale for every visit.

Longitudinal distribution of psychiatric pathology in research branches comparative to witness branches was illustrated in tables 10.1 – 10.6.

Patients showing psychiatric manifestations (anxiety, depression, psychosis, delusions, mania, hipomania, bipolar depression) in different visits received psychiatric chemotherapy - monotherapy or augmentative treatment according to pathology.

Vizita	V0 (Inițială)	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Determinare înălțime, greutate	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	X
Viremie	x			x			x				x		x					x
Puncție biopsie hepatică	x								x									
Analize de sânge uzuale (ALAT, ASAT)	x			x			x				x							x
Consimțământ informat	x																	
Interviu clinic general	x																	
Interviu psihiatric	x																	
Scale evaluare																		
HAMD	x			x			x				x		x					x
MADRS	x			x			x				x		x					x
COVI	x			x			x				x		x					x
ZUNG (ae)	x			x			x				x		x					x
HAMA	x			x			x				x		x					x

Tabelul 10.1. Schema studiului

Vizita	V0 (Inițială)	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
YMRS	x			x			x				x		x					x
MMSE	x			x			x				x		x					x
HQL	x			x			x				x		x					x
PANSS	x			x			x				x		x					x
SOFAS	x			x			x				x		x					x
Efecte adverse	x			x			x				x		x					x

Tabelul 10.1. Schema studiului (continuare)

Vizita	V0 (Iniţială)	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Depresie uşoară	30	19	25	29	30	28	25	20	22	20	20	20	18	15	10	7	9	5
Depresie medie	7	8	7	7	6	5	5	6	5	7	6	5	4	5	3	4	3	3
Depresie severă	2	1	1	0	1	1	1	0	0	1	0	0	1	0	1	0	0	0
Depresie severă cu elemente psihotice	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1
Hipomanie	3	2	1	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0
Manie	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0
Tulburare psihotică	1	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Deficit cognitiv	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sindrom diskinetic	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Anxietate	35	30	25	15	15	17	15	10	10	10	12	10	12	10	11	10	9	7
Efecte adverse	-	50	45	48	44	30	25	22	17	10	10	9	8	8	8	7	6	5

Tabelul 10.2. Patologia psihiatrică – lot 85 de pacienţi trataţi cu Roferon şi ribavirină

Vizita	V0 (Iniţială)	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Depresie uşoară	19	18	15	15	17	14	15	17	17	16	15	15	14	14	10	11	10	9
Depresie medie	9	7	8	7	7	5	6	7	6	5	5	5	6	5	5	5	3	0
Depresie severă	7	5	5	4	4	5	3	3	2	3	2	2	1	2	2	0	1	1
Depresie severă cu elemente psihotice	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Hipomanie	4	3	2	2	1	1	1	1	1	1	2	1	1	1	1	1	1	1
Manie	1	0	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	1
Tulburare psihotică	3	2	2	2	2	3	2	1	1	0	0	0	0	0	0	2	1	1
Deficit cognitiv	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sindrom diskinetic	0	0	1	2	1	1	1	1	2	1	1	1	2	1	1	1	1	1
Anxietate	25	20	15	15	17	16	15	15	12	12	11	10	10	9	7	8	8	9
Efecte adverse	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Tabelul 10.3. Patologia psihiatrică – lot martor

Vizita	V0 Inițială	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Determinare înălțime, greutate	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Viremie	x			x			x				x		x					x
Puncție biopsie hepatică	x								x									
Analize de sânge uzuale (ALAT, ASAT)	x			x			x				x							x
Consimțamânt informat	x																	
Interviu clinic general	x																	
Interviu psihiatric	x																	
Scale evaluare																		
HAMD	x			x			x				x		x					x
MADRS	x			x			x				x		x					x
COVI	x			x			x				x		x					x
ZUNG (ae)	x			x			x				x		x					x
HAMA	x			x			x				x		x					x

Tabelul 10.4. Schema studiului – Pegasys şi ribavirină

Vizita	V0 (Inițială)	V1 - 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
YMRS	x			x			x				x		x					x
MMSE	x			x			x				x		x					x
HQL	x			x			x				x		x					x
PANSS	x			x			x				x		x					x
SOFAS	x			x			x				x		x					x
Efecte adverse	x			x			x				x		x					x

Tabelul 10.4. Schema studiului – Pegasys şi ribavirină (continuare)

Vizita	V0 (Iniţială)	V1 – 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Depresie uşoară	35	20	25	25	33	27	25	20	23	23	20	20	15	15	14	12	12	12
Depresie medie	10	9	8	8	7	6	5	5	6	7	6	5	5	5	4	4	3	3
Depresie severă	5	5	4	4	3	3	3	2	2	2	2	1	1	1	1	1	1	1
Depresie severă cu elemente psihotice	1	1	1	1	1	1	1	0	1	0	0	0	1	0	0	0	0	0
Hipomanie	5	4	4	3	3	1	1	0	1	0	0	0	1	0	0	0	0	0
Manie	1	1	1	1	0	1	1	1	0	0	1	1	0	0	0	0	0	0
Tulburare psihotică	1	1	1	1	1	1	1	0	0	1	0	1	1	1	1	1	1	0
Deficit cognitiv	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sindrom diskinetic	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Anxietate	45	42	30	35	33	30	25	20	20	17	18	15	15	14	12	11	10	10
Efecte adverse	-	48	43	42	44	37	32	28	24	20	17	14	12	11	9	7	8	8

Tabelul 10.5. Patologia psihiatrică – lot 100 de pacienţi trataţi cu Pegasys şi ribavirină

Vizita	V0 (Iniţială)	V1 – 1 lună	V2 – 2 luni	V3 – 3 luni	V4 – 4 luni	V5 – 5 luni	V6 – 6 luni	V7 – 9 luni	V8 – 12 luni	V9 – 15 luni	V10 – 18 luni	V11 – 21 luni	V12 – 24 luni	V13 – 27 luni	V14 – 30 luni	V15 – 33 luni	V16 – 36 luni	V17 – 42 luni
Depresie uşoară	39	37	35	30	25	24	20	22	20	25	26	25	20	20	17	14	12	10
Depresie medie	14	15	15	14	14	12	10	9	8	10	11	12	15	18	20	16	12	11
Depresie severă	8	7	5	5	5	5	5	5	2	4	5	2	3	5	7	8	10	10
Depresie severă cu elemente psihotice	1	1	1	1	1	1	0	0	0	1	0	1	0	0	0	1	2	2
Hipomanie	5	5	3	3	2	2	1	1	1	1	1	1	1	1	1	1	1	1
Manie	1	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1
Tulburare psihotică	4	3	3	2	2	3	2	1	0	1	0	0	0	0	0	2	2	2
Deficit cognitiv	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sindrom diskinetic	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Anxietate	20	18	19	17	16	16	15	14	12	12	11	11	10	10	8	8	8	9
Efecte adverse	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Tabelul 10.6. Patologia psihiatrică – lot martor

Chapter XI

Results and Discussions

Statistics opperate with concepts about characteristics of a multitude of elements. Purpose is analizing characteristic data for a certain process and establishing a pattern for further phenomenon evolution.

Psychiatric symptoms evolution of research branches patients (chapter 10) was analized using evaluation scales (presented in chapter V).

1 Hamilton Depression Rating Scale – HAM –D

HAM – D patients evaluation in research design results in the following outcome.

Lot PR	V0	V3	V6	V10	V12	V17
Episod maniacal si hipomaniacal	6	4	2	1	1	0
Depresie usoara	35	25	25	20	15	12
Depresie moderata	10	8	5	6	5	3
Depresie severa fara elemente psihotice	5	4	3	2	1	1
Depresie severa cu elemente psihotice	1	1	1	0	1	0
Echilibrare	43	58	64	71	77	84

Table 11.1 PR Research Branch Evolution According to HAM – D

Lot PRM	V0	V3	V6	V10	V12	V17
Episod maniacal si hipomaniacal	6	3	1	1	1	2
Depresie usoara	39	30	20	26	20	10
Depresie moderata	14	14	10	11	15	11
Depresie severa fara elemente psihotice	8	5	5	5	3	10
Depresie severa cu elemente psihotice	1	1	0	0	0	2
Echilibrare	32	47	64	57	61	65

Table 11.2 PRM Witness Branch Evolution According to HAM – D

Lot RR	V0	V3	V6	V10	V12	V17
Episod maniacal si hipomaniacal	3	1	2	0	0	0
Depresie usoara	30	29	25	20	18	5
Depresie moderata	7	7	5	6	4	3
Depresie severa fara elemente psihotice	2	0	1	0	1	0
Depresie severa cu elemente psihotice	1	0	0	0	0	1
Echilibrare	42	48	52	59	62	76

Table 11.3 RR Research Branch Evolution According to HAM – D

Lot RRM	V0	V3	V6	V10	V12	V17
Episod maniacal si hipomaniacal	5	2	1	2	2	2
Depresie usoara	19	15	15	15	14	9
Depresie moderata	9	7	6	5	6	0
Depresie severa fara elemente psihotice	7	4	3	2	1	1
Depresie severa cu elemente psihotice	1	0	0	0	0	2
Echilibrare	44	57	60	61	62	71

Table 11.4 RRM Witness Branch Evolution According to HAM – D

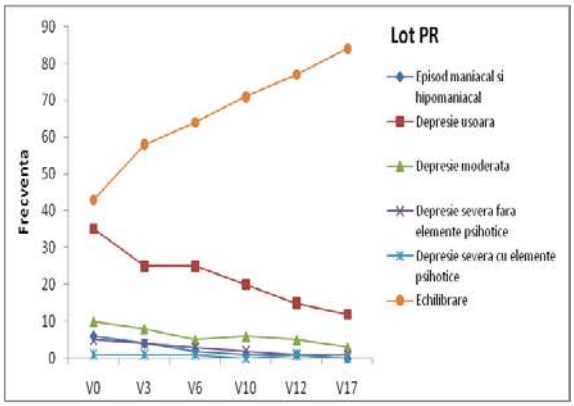

Figure 11.1 PR Research Branch Evolution According to HAM – D

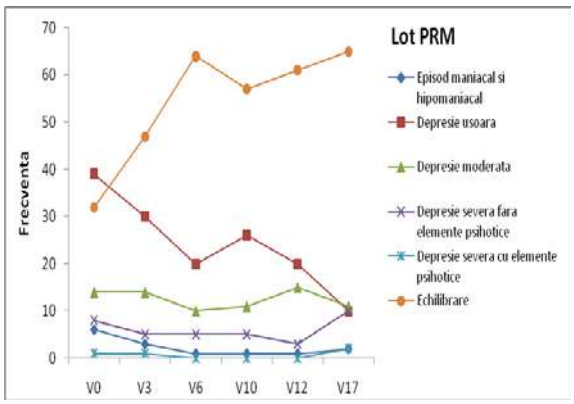

Figure 11.2 PRM Witness Branch Evolution According to HAM – D

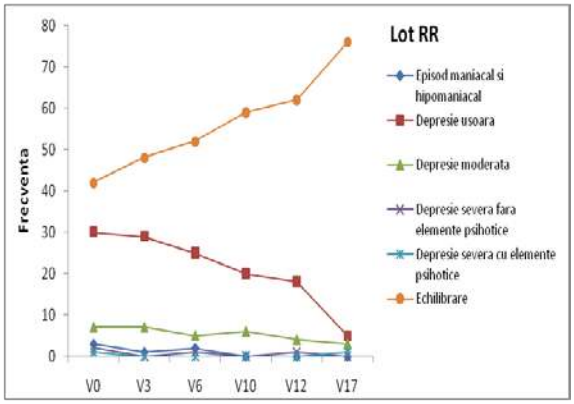

Figure 11.3 RR Research Branch Evolution According to HAM – D

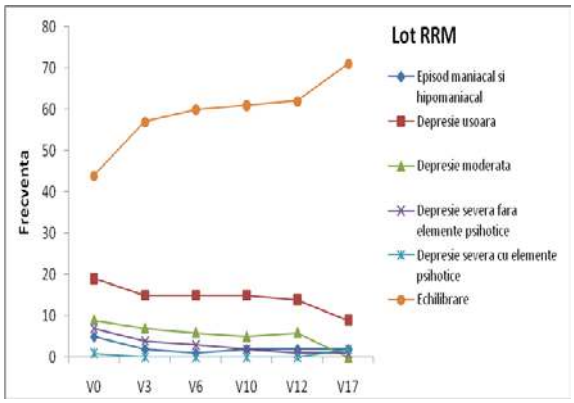

Figure 11.4 RRM Witness Branch Evolution According to HAM – D

The branches evolution in HAM – D testing comes as follows:

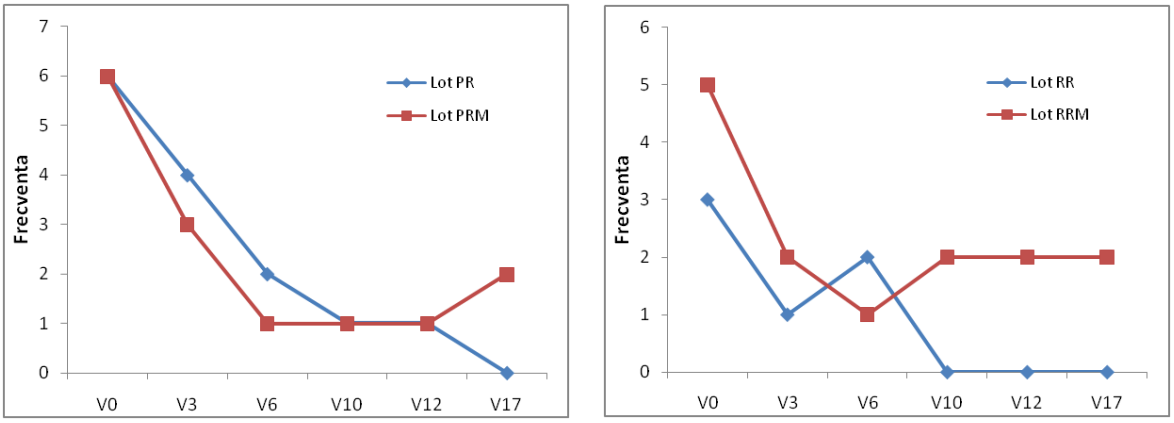

Figure 11.5 Manic and Hipomanic Episodes in HAM – D Evaluation

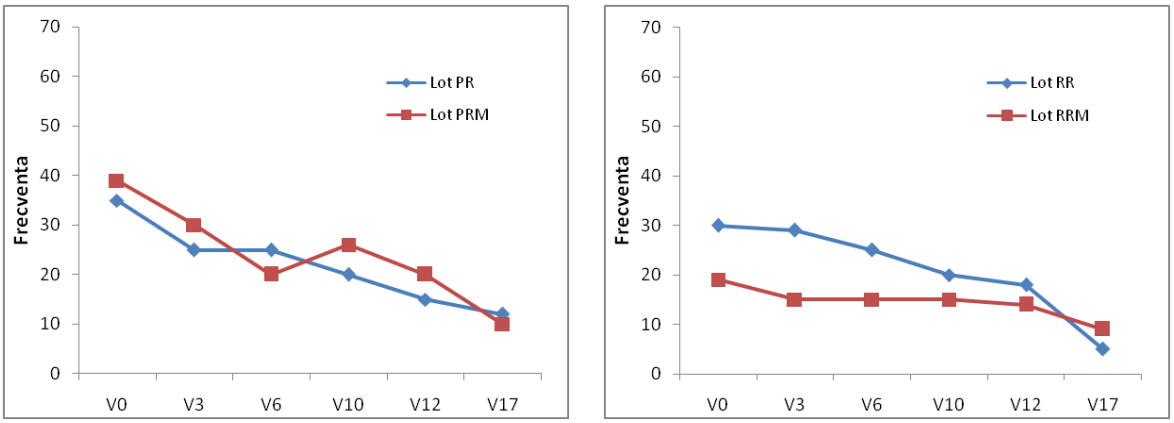

Figure 11.6 Mild Depression in HAM – D Evaluation

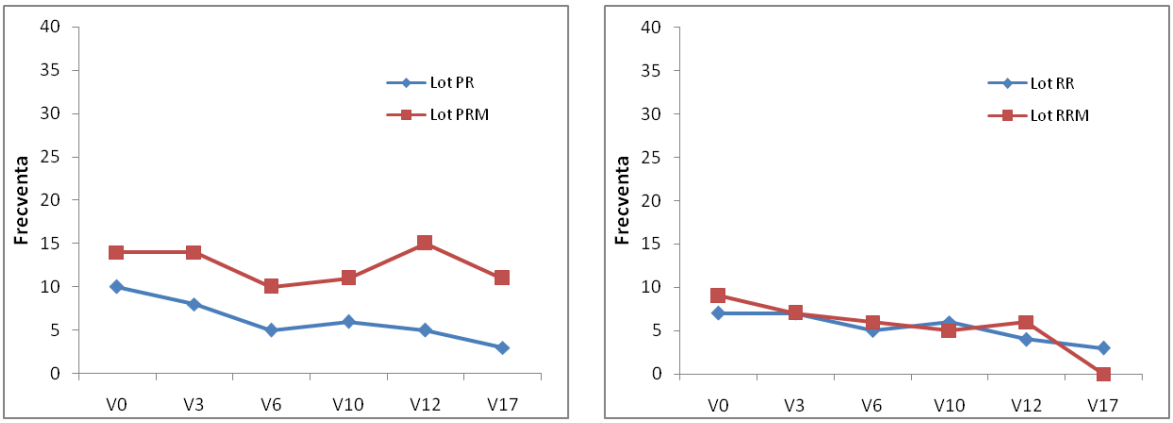

Figure 11.7 Moderate Depression in HAM – D Evaluation

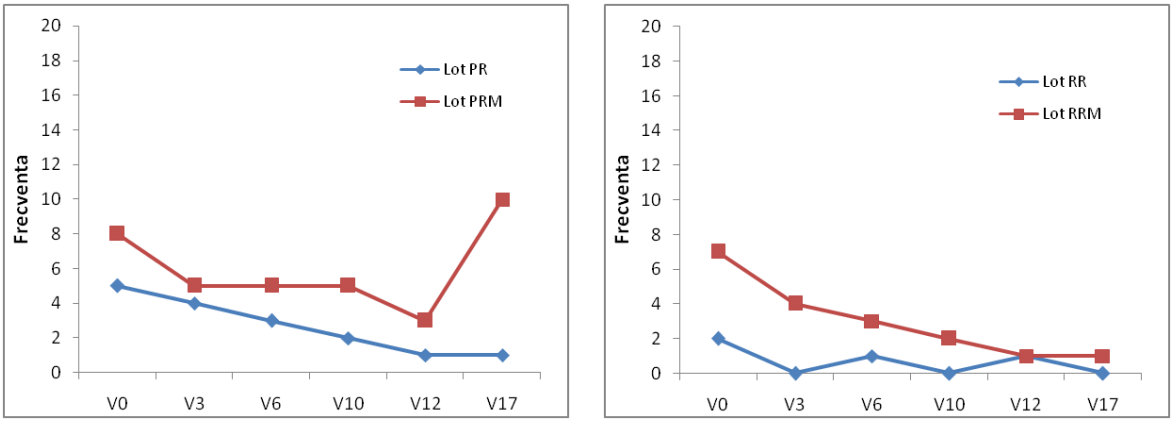

Figure 11.8 Severe Depression without Psychotic Elements in HAM – D Evaluation

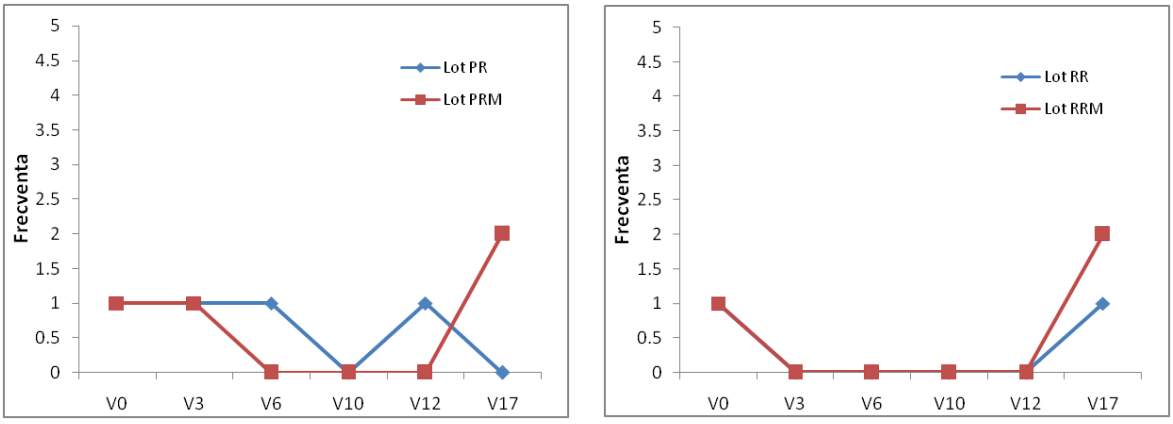

Figure 11.9 Severe Depression with Psychotic Elements in HAM – D Evaluation

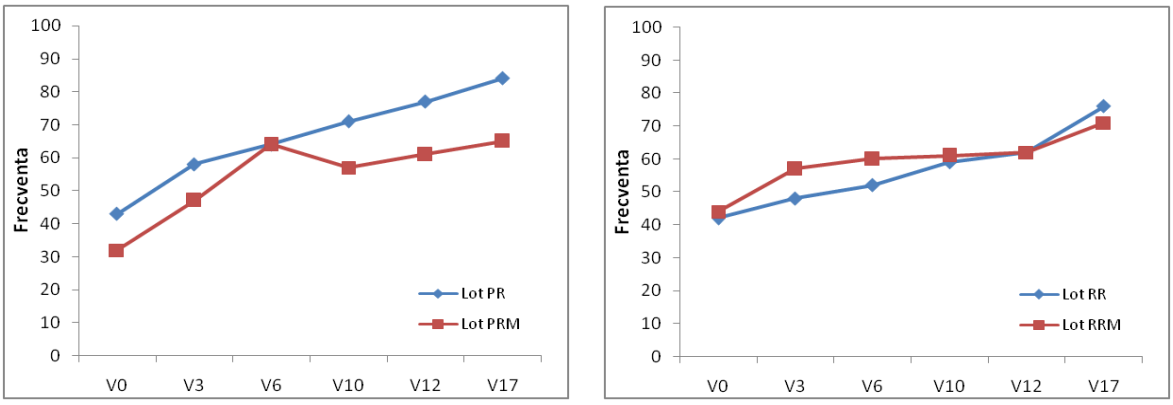

Figure 11.10 Stabilization (Equilibrium) in HAM – D Evaluation

Score Interpretation of HAM - D Evaluation

Manic and Hipomanic Episodes in HAM – D Evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	0.00	0.00	0.00
V3	1.00	0.58	0.33
V6	1.00	1.00	1.00
V10	0.00	0.00	0.00
V12	0.00	0.00	0.00
V17	-2.00	-1.41	2.00

CHI^2 calc	3.33	**3.33**
p	**0.649**	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	-2.00	-0.89	0.80
V3	-1.00	-0.71	0.50
V6	1.00	1.00	1.00
V10	-2.00	-1.41	2.00
V12	-2.00	-1.41	2.00
V17	-2.00	-1.41	2.00

CHI^2 calc	8.30	**8.30**
p	**0.140**	
df	5	
CHI^2 cr	11.07	

Table 11.5 χ^2 Test For Manic and Hipomanic Episodes in HAM – D Evaluation

PR - PRM

Because $\chi^2_{calc} = 3{,}33$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} < \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}649$ and $\alpha = 0{,}05 \implies p > \alpha$ there are no significant differences in spread of pacients with manic and hipomanic episodes for similar visits of PR research branch and PRM witness branch.

RR - RRM

Because $\chi^2_{calc} = 8{,}3$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} < \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}140$ and $\alpha = 0{,}05 \implies p > \alpha$ there are no significant differences in spread of pacients with manic and hipomanic episodes for similar visits of RR research branch and RRM witness branch.

Mild depression in HAM – D Evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	-4.00	-0.64	0.41
V3	-5.00	-0.91	0.83
V6	5.00	1.12	1.25
V10	-6.00	-1.18	1.38
V12	-5.00	-1.12	1.25
V17	2.00	0.63	0.40

CHI^2 calc	5.53	**5.53**
p	**0.355**	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	11.00	2.52	6.37
V3	14.00	3.61	13.07
V6	10.00	2.58	6.67
V10	5.00	1.29	1.67
V12	4.00	1.07	1.14
V17	-4.00	-1.33	1.78

CHI^2 calc	30.69	**30.69**
p	**0.000**	
df	5	
CHI^2 cr	11.07	

Table 11.6 χ^2 Test for Mild Depression in HAM – D Evaluation

PR - PRM

Because $\chi^2_{calc} = 5{,}53$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} < \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}355$ and $\alpha = 0{,}05 \implies p > \alpha$ there are no significant differences in spread of patients with mild depression for similar visits of PR research branch and PRM witness branch.

RR - RRM

Because $\chi^2_{calc} = 30{,}69$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p < 0{,}001$ and $\alpha = 0{,}05 \implies p < \alpha$ there are significant differences in spread of pacients with moderate depression for similar visits of RR research branch and RRM witness branch. Because $|Re - s_0| = 2{,}52 > 2$, $|Re - s_3| = 3{,}61 > 2$ and $|Re - s_6| = 2{,}58 > 2$ significant differences are in visits *V3*, *V6* şi *V0* with major share in final results.

Moderate Depression in HAM - D Evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	-4.00	-1.07	1.14
V3	-6.00	-1.60	2.57
V6	-5.00	-1.58	2.50
V10	-5.00	-1.51	2.27
V12	-10.00	-2.58	6.67
V17	-8.00	-2.41	5.82

CHI^2 calc	20.97	20.97
p	0.001	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	-2.00	-0.67	0.44
V3	0.00	0.00	0.00
V6	-1.00	-0.41	0.17
V10	1.00	0.45	0.20
V12	-2.00	-0.82	0.67
V17	3.00	299.99	89994.00

CHI^2 calc	#NUM!	89995.48
p	0.000	
df	5	
CHI^2 cr	11.07	

Tabelul 11.7 χ^2 Test for Moderate Depression in HAM – D Evaluation

PR - PRM

Because $\chi^2_{calc} = 20{,}97$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}001$ and $\alpha = 0{,}05 \implies p < \alpha$ there are significant differences in spread of pacients with moderate depression for similar visits of PR research branch and PRM witness branch. Because $|Re - s_{12}| = 2{,}58 > 2$ and $|Re - s_{17}| = 2{,}41 > 2$ significant differences are in visits *V12* şi *V17* with major share in final results.

RR - RRM

Because χ^2_{calc} is an extremely high value and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p < 0{,}001$ and $\alpha = 0{,}05 \implies p < \alpha$ there are significant differences in spread of pacients with moderate depression for similar visits of RR research branch and RRM witness branch. Because $|Re - s_{17}| = 299{,}99 > 2$ significant differences are in *V17* visit with major share in final results.

Severe Depression without Psychotic Elements in HAM - D evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	-3.00	-1.06	1.13
V3	-1.00	-0.45	0.20
V6	-2.00	-0.89	0.80
V10	-3.00	-1.34	1.80
V12	-2.00	-1.15	1.33
V17	-9.00	-2.85	8.10

CHI^2 calc	13.36	13.36
p	0.020	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	-5.00	-1.89	3.57
V3	-4.00	-2.00	4.00
V6	-2.00	-1.15	1.33
V10	-2.00	-1.41	2.00
V12	0.00	0.00	0.00
V17	-1.00	-1.00	1.00

CHI^2 calc	11.90	11.90
p	0.036	
df	5	
CHI^2 cr	11.07	

Tabelul 11.8 χ^2 Test for Severe Depression without Psychotic Elements in HAM – D Evaluation

PR - PRM

Because $\chi^2_{calc} = 13{,}36$ and $\chi^2_{cr} = 11{,}07 \Rightarrow \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}020$ and $\alpha = 0{,}05 \Rightarrow p < \alpha$ there are significant differences in spread of pacients suffering of depression without psychotic elements for similar visits of PR research branch and PRM witness branch. Because $|Re - s_{17}| = 2{,}85 > 2$ significant differences are in *V17* visit with major share in final results.

RR - RRM

Because $\chi^2_{calc} = 11{,}90$ and $\chi^2_{cr} = 11{,}07 \Rightarrow \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p < 0{,}036$ şi $\alpha = 0{,}05 \Rightarrow p < \alpha$ there are significant differences in spread of pacients suffering of severe depression without psychotic elements for similar visits of RR research branch and RRM witness branch. Because $|Re - s_3| = 2$ significant differences are in *V3* visit with major share in final results.

Severe Depression with Psychotic Elements in HAM - D Evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	0.00	0.00	0.00
V3	0.00	0.00	0.00
V6	1.00	99.99	9998.00
V10	0.00	-0.01	0.00
V12	1.00	99.99	9998.00
V17	-2.00	-1.41	2.00

CHI^2 calc	#NUM!	19998.00
p	0.000	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	0.00	0.00	0.00
V3	0.00	0.00	0.00
V6	0.00	0.00	0.00
V10	0.00	0.00	0.00
V12	0.00	0.00	0.00
V17	-1.00	-0.71	0.50

CHI^2 calc	0.50	0.50
p	0.992	
df	5	
CHI^2 cr	11.07	

Table 11.9 χ^2 Test for Severe Depression with Psychotic Elements in HAM – D evaluation

PR - PRM

Because χ^2_{calc} is an extremely high value and $\chi^2_{cr} = 11{,}07 \Rightarrow \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p < 0{,}001$ and $\alpha = 0{,}05 \Rightarrow p < \alpha$ there are significant differences in spread of pacients suffering of severe depression with psychotic elements for similar visits of PR research branch and PRM witness branch. Because $|Re - s_6| = 99{,}99 > 2$ and $|Re - s_{12}| = 99{,}99 > 2$ differences are significant in *V6* şi *V12* visits with major share in final results.

RR - RRM

Because $\chi^2_{calc} = 0{,}5$ and $\chi^2_{cr} = 11{,}07 \Rightarrow \chi^2_{calc} < \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}992$ and $\alpha = 0{,}05 \Rightarrow p > \alpha$ there are no signifcant differences in spread of pacients suffering of severe depression with psychotic elements for similar visits of RR research branch and RRM witness branch.

Stabilization (Equilibrium) in HAM - D Evaluation

Lot PR - Lot PRM			
Vizita	Re	Re-s	
V0	11.00	1.94	3.78
V3	11.00	1.60	2.57
V6	0.00	0.00	0.00
V10	14.00	1.85	3.44
V12	16.00	2.05	4.20
V17	19.00	2.36	5.55

CHI^2 calc	19.54	19.54
p	0.002	
df	5	
CHI^2 cr	11.07	

Lot RR - Lot RRM			
Vizita	Re	Re-s	
V0	-2.00	-0.30	0.09
V3	-9.00	-1.19	1.42
V6	-8.00	-1.03	1.07
V10	-2.00	-0.26	0.07
V12	0.00	0.00	0.00
V17	5.00	0.59	0.35

CHI^2 calc	3.00	3.00
p	0.701	
df	5	
CHI^2 cr	11.07	

Table 11.10 χ^2 Test for Stabilization (Equilibrium) in HAM – D Evaluation

PR - PRM

Because $\chi^2_{calc} = 19{,}54$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} > \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}002$ and $\alpha = 0{,}05 \Longrightarrow p < \alpha$ there are significant differences in spread of stabilized pacients for similar visits of PR research branch and PRM witness branch. Because$|Re - s_{12}| = 2{,}05 > 2$ and $|Re - s_{17}| = 2{,}36 > 2$ differences are significant in *V17* and *V12* visits with major share in final results.

RR - RRM

Because $\chi^2_{calc} = 3{,}00$ and $\chi^2_{cr} = 11{,}07 \implies \chi^2_{calc} < \chi^2_{cr}$, $(df = 5)$ respectively $p = 0{,}701$ and $\alpha = 0{,}05 \Longrightarrow p > \alpha$ there are no signifcant differences in spread of stabilized pacients for similar visits of RR research branch and RRM witness branch.

Similar statistic calculus were performed for symptoms evaluation using clinical scales. Conclusions were elaborated considering these calculus.

Chapter XII

Conclusions

Discutions

Patients infected with B or C viruses in treatment with interferon and ribavirine expressed various psychiatric disorders with different intensity of symptoms. In some cases, interferon treatment was interrupted temporarily or definitive, and psychiatric treatment was given in conditions of hospitalization or ambulatory.

Among patients in the research branches, 45% expressed depressive spectrum disorders of different intensities, similar data with actual other research results.

Other researches' conclusions are similar with the data in our present research.

Depressive symptoms were generally in the limits of disease's duration, specific treatment ameliorated the symptoms confirmed by clinical scales evaluation.

Among patients in the witness branches (infected patients but not receiving interferon due to various situations) 20% to 25% expressed depressive spectrum disorders. Viral infection inducing depression theory was considered.

Initially, interferon discontinuation rate was 20%, some patients continuated with interferon and with psychiatric treatment.

Anxious disorders were found in 30% of patients who received specific psychiatric treatment and continuated interferon treatment, similar data with actual other research results.

Anxious disorders were found also in 20% of the patients in witness branches(infected patients but not receiving interferon due to various situations) sugesting viral infection inducing anxiety disorders.

Manic and hipomanic patients (5%) received specific stabilizing therapy and continuated or restarted interferon therapy.

Manic or hipomanic episodes occuring in 2% of witness branch (infected patients but not receiving interferon due to various situations)patients received specific psychiatric treatment and ameliorated. A possible viral infection contribution in mood disorders etiology was considered also.

Psychotic patients with or without schizophrenia-like symptoms had psychiatric antipsychotic treatment for a considerable period of time and 50% mainteined interferon treatment rate. Psychotic patients were monitored for a long period of time (between one and three years).

Whiteness branches patients who did not had interferon treatment developped also various psychiatric disorders with different degrees of intensity.The proportion was slightly increased compared with the prevalence in general population (1%) They received psychiatric specific treatment and they were followed-up for a long period of time also. suggesting a possible infectious contribution in psychosis etiology.

Establishing associated vulnerability factors inducing psychiatric disorders in infected pacients treated with interferon is a useful tool for a better therapy.

Clinical guidelines scketching based upon practic experience and statistics improves therapeutical conduct, psychiatric treatment in patients infected with hepatic viruses and treated with interferon.

Fullfilling Objectives
Results and Limits

1. Proposing psychiatric "pre-treatment" using SSRI drugs (Selective Serotonine Re-uptake Inhibitors) in infected patients with high scores for depression on clinical scales and with first or second degree relatives suffering of mood disorders. The patients must consent to the treatment. Initially, treatment duration is for three months. Psychotherapy can be associated. Depressive symptoms ameliorate and interferon treatment is continuated or given back if stopped. Interferon therapy adverse effects are diminished in intensity and duration for patients receiving antidepressive therapy comparative with those who did not.

If a depressive relapse occur, the treatment is for another six months, if a second relapse occur the tratment is for one year. If the patient relapses again, the treatment is for unlimited duration.

2. Proposing psychiatric "pre-treatment" using SSRI drugs (Selective Serotonine Re-uptake Inhibitors) combined with anxiolitic drugs (augmentative treatment) in infected patients with high scores for depression and anxiety on clinical scales. The patients must consent to the treatment, also. Initially, treatment duration is for three months. Psychotherapy can be associated. Depressive and anxious symptoms ameliorate and interferon treatment is continuated or given back if stopped. Future anxious and depressive symptoms are non significant for those treated with SSRI and anxiolitic drugs. If a depressive and anxious relapse occurr, the treatment is for another six months, if a second relapse occurr the tratment is for one year. If the patient relapses again, the treatment is for unlimited duration. Interferon treatment is maintained as needed in all that time.

3. Proposing mood stabilizer "pre-treatment" (second generation antipsychotics or valproic acid and valproat) in patients diagnosed with hepatic B or C viral infection with significant scores on specific mania (hypomania) scales (YMRS Young Mania Rating Scale). Initially, treatment duration is for three months. Psychotherapy can be associated also. Manic, hypomanic and bipolar spectrum symptoms ameliorate under mood stabilizer or second generation antipsychotics (atipical antipsychotics). Interferon treatment is continuated or given back if stopped. Future symptoms are non significant for the treated patients. Patients will be monitored during interferon treatment and after that. If another manic or severe depressive episode occurr, mood stabilizer tratment is given unlimited duration.

Patients will be monitored during interferon treatment and after.

Antidepressats, anxiolitic drugs and/or antipsychotics will be tapered down. Maintenance treatment (minimum therapeutic dosages) will be cosidered in order to avoid liver toxicity. Psychiatric symptoms will be monitored as well as blood values metabolites. Relapse during interferon cure or after will be treated as an acute episode for at least six months. Follow-up period will be considered also.

4. SSRI treatment in medium dosages will be considered for infected patients expressing depressive symptoms confirmed by clinical scales testing. In the begining the treatment will last for three months; a second relapse will be treated for six months and the third relapse will be treated for unlimited period of time. Interferon or interferon combined with ribavirine treatment will be mainteined.

Augmentative antidepressive treatment (SSRI-s and anxiolitic drugs) will be administrated for three months initially. A new relapse will be treated for six months; at the third relapse augmentative treatment will be recommended for an year. Further relapses will be treated for unlimited period of time. Interferon or interferon combined with ribavirine treatment will be mainteined.

Antimanic treatment (second generation antipsychotics or mood stabilizers as valproate or valproic acid) in association or not with benzodiazepines for manic or hipomanic infected patients will be recomended for at least six months concomitant with interferon treatment. If a new manic or hipomanic eoisode occures, antimanic treatment will be maintained for unlimited duration in association with interferon or interferon and ribavirine.

For mood disorderd noncompliant patients to daily oral medication, parentheral long acting drugs are reccomended, doses being adjusted to symptoms' intensity (Rispolept consta 25mg, 37,5 mg and 50 mg., ZypAdhera 210 mg, 300 mg and 405mg). Treatment administration is one or twice monthly. Patient must consent. Clinical and psychiatric monitoring is considered in condition of continuing interferon (and ribavirine) treatment. Parentheral treatment is avoiding first liver pass comparative to oral medication.

Psychotic patients are given antipsychotic treatment (second generation antipsychotic drugs) in monotherapy or associated or antipsychotic drug associated with antidepressants, mood stabilizers and benzodiazepines, according to intensity and duration of symptoms. Interferon (and ribavirine) therapy is possible. After a "loading" period of time, antidepressive, anxiolitic, antipsychotic treatment is decreased gradually to maintenance level (minimum efficient dose), in order to preserve liver function. Psychiatric symptoms and liver functioning are monitored. If liver functioning is affected during or after interferon treatment, doses and treatment duration will be adjusted (proposed duration for treatment after relapse is six months).

For psychotic noncompliant patients to daily oral medication, parentheral long acting drugs are reccomended, doses being adjusted to symptoms' intensity (Rispolept consta 25mg, 37,5 mg and 50 mg, ZypAdhera 210 mg, 300 mg and 405mg). Treatment administration is one or twice monthly. Patient must consent. Clinical and psychiatric monitoring is considered in condition of continuing interferon (and ribavirine) treatment.

Psychiatric treatment is given apart interferon treatment for infected patients with psychiatric symptoms. Only monitoring psychiatric symptoms and liver function can give therapeutic indicationindividualized for each case.

Direct costs are represented by antiviral medication costs (interferon or interferon and ribavirine) added to psychiatric medication costs (antidepressants, anxiolitic drugs, antipsychotics, mood stabilizers). Invalidity period payements, hospitalization fees and pensions are also included in disease's costs. Maintenance treatment costs after acute phase are also added. Both diseses being part of national programmes in our country, patients do not pay directly.

Indirect costs are caused by work incapacity and decrease of work productivity. Evaluation of indirect costs is difficultand interpretable.

5. Peculiar cases

Peculiar cases met can be classificated as follows:

– anxious patients with the onset of psychiatric symptoms after liver infection was confirmed by specific tests. Anxious symptoms ameliorate under anxiolitic and antidepressant SSRI or augmentative (combined) treatment before starting interferon treatment. Anxious symptoms are under control and are not significant after the treatment was stopped;

– anxious patients with the onset of psychiatric symptoms after liver infection was confirmed by specific tests. Anxious symptoms ameliorate under anxiolitic and antidepressant SSRI or augmentative (combined) treatment before starting interferon treatment. After that, anxiety is intense again and anxiolitic and antidepressant treatment are administered again;

– anxious patients with the onset of psychiatric symptoms during interferon treatment. Anxious symptoms are under control and are not significant after the treatment was stopped;

– anxious patients with the onset of psychiatric symptoms during interferon treatment; anxious symptoms are under control for a while but get more intense afterwards; psychiatric therapy is administered again, each relapse imposing a longer duration of therapy;

– depressive patients with the onset of depressive symptoms before viral infection was confirmed; depressive symptoms ameliorate under antidepressant medication before starting interferon treatment; depressive symptoms are under control and are not significant after the treatment was stopped;

– depressive patients with the onset of depressive symptoms after viral infection was confirmed; depressive symptoms ameliorate under antidepressant medication until interferon treatment starts; after that, depressive symptoms' intensity increases again and antidepressant treatment is administered again; interferon tratment (and ribavirine) is prezerved;

– depressive patient with the onset of depressive symptoms after interferon cure is ended; depressive symptoms ameliorate under treatment, few patients will express chronic depressive features;

– manic or hypomanic patients with the onset of symptoms after infection is confirmed; symptoms are remited under specific mood stabilizer antimanic treatment (second generation antipsychotic drugs in association or not with valproic acid and valproate); during interferon cure manic symptoms are intense again and psychiatric treatment is needed again for a longer period of time;

– manic or hypomanic patients with the onset of symptoms after interferon cure is finished, imposing repeated antimanic treatment or unlimited duration maintenance treatment with long acting antipsychotics;

– manic or hypomanic patients remitted under psychiatric treatment; after that, a depressive episode occurr, the so called "bipolar depression" with specific treatment antidepressant and antipsychotic or valproic acid and valproate as mood stabilizer or clonazepam (24 ours effect); antidepressants without mood stabilizers can induce the so called "swich" to manic or hipomanic episode;

– psychotic symptoms with the onset during interferon cure and treated with antipsychotics mainteining interferon treatment; after psychiatric treatment was stopped a relapse occurred and antipsychotic treatment was needed again; after 2-3 psychiatric relapses treated with antipsychotics, the patient is stabilized and will be followed - up;

– psychotic symptoms with the onset after interferon cure and treated with antipsychotics as maintenance therapyfor a long period of time; liver function and infection will be periodically evaluated;

6. Follow-up metodology implements follow-up visits at six months after interferon cure is finished or when a relapse occurr. Psychiatric follow-up and liver function evaluation are important targets. Complication identified are treated. Follow-up skedule is rigurously but flexible. A common data base for both specialities is useful for psychiatrist and for gastroenterologist. Patient are instructed

to recognize modifications in their health condition and to signal that in order to prevent further complications.

7. When complications occur (cirrhosis, adenocarcinoma, psychiatric relapses), the case will be analyzed and reevaluated by psychiatrist and gastroenterologist, and the best solution will be adopted. If one of the two diseases is ameliorate and the other is still active, the treatment will be centered on it for a better remission. Treatment is individualized in each cas

Conclusions

B and C hepatic virus infected patients treated with interferon with cytokine-like action can express various spectrum psychiatric disorders, most frequent anxiety, depression and bipolar spectrum disorders (mania, hypomania). These psychiatric disorders manifest in infected patients not treated with interferon suggest a possible viral implication in psychopathology. Psychotic disorders, delusional disorders, cognitive impairment and diskynezia are also mentioned.

Patients treated with interferon in association with ribavirine express more psychiatric disorders than patients treated only with interferon. Interferon has cytokine-like action, amplifying pathological reactions directly and indirectly. In the same time, viral infection can induce psychiatric symptoms and the need for psychiatric treatment for patients in witness branches (infected patients but not treated with interferon). Hepatic viruses are infecting also the central nervous cells.

Psychiatric pre-treatment in vulnerable for psychiatric disorders and infected patients in need for interferon treatment also can prevent onset and exacerbation of psychiatric disorders making possible a correct therapy for hepatitis. Interferon treatment can be administrated.

Psychiatric treatment administered for psychotic episode concomitant with interferon treatment discontinuation makes possible remission of psychotic episode and restarting interferon administration.

Follow-up and clinical monitoring through periodic psychiatric scales evaluation and lab tests allow the most appropriate therapeutic intervention in order to ensure the best evolution and prognosis.

Patient's and patient's family psycho education helps them understand and assuming clinical issues and represent the best solution for better results and an improved quality of life with minimum cost.

Simple supportive psychotherapy, group therapy and family therapy represent useful intervention tools combined with antiviral treatment and psychiatric medication.

Interdisciplinary collaboration between the two medical disciplines involved psychiatry and internal medicine-gastroenterology and team work insure optimum therapeutic intervention in each situation, considering also peculiarities.

Patients follow-up after finishing interferon cure and after stopping psychiatric treatment can prevent relapses and complications, allowing prompt intervention in due time.

Database maintaining and monitoring – follow-up – can offer valuable contribution and the possibilities of specific and palliative in terminal patients. Family support is also possible for the optimum case management.

Clinicians expertise resulted in cases management activity can establish *patterns* for the comorbid illnesses. Similar and predictible patterns of outcome and treatment response are useful tools for the optimum management of comorbid *psychiatric disorders* related to *interferon treated chronic hepatitis*.

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