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Interferon-Beta-1a (Rebif) a Risk Factor on Liver, Kidney and Sex Hormones with Multiple Sclerosis Patients: A Review

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Annotation: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (C.N.S). It is an autoimmune degenerative disease characterized by damage to the insulating myelin sheath covering the axons of the brain and spinal cord, often leading to a state of disability. The management of MS remains a major challenge.

Interferon beta (IFN-β) is one of the most important licensed treatments for disease-modifying MS. interferon acts as an immunomodulation by reducing antigen presentation and T - cells. enhancing suppressor reducing pro - inflammatory cytokines, and Lymphocyte suppression migration in CNS. I.FN-β is a relatively effective Freedom of choice. Medication for patients with M.S. However, this treatment has multiple side effects, Including reactions at the injection site liver, dysfunction, decreased peripheral blood cell counts, and worsening depression. Its immunological characteristics and the genetic diversity of patients are associated with variability in response. Current review will discuss the various said effectes of interferon beta (IFN-β) at liver, kidney function at multiple sclerosis patients. The review focuses on the extent to which interferon (IFN-I) damages liver and kidney tissue, directly impacting the biology and function of many types of diseases. of

kidney and liver cells. It also discusses the extent to which male and female sex hormone levels are affected, especially during pregnancy in women with MS are treatment by interferon repeatedly weekly for long periods.

Conclusion: The review concluded that long-term and repeated interferon therapy has significant effects on patients with multiple sclerosis, especially on liver and kidney tissues, as well as on fetuses in pregnant women, especially in the last stages of pregnancy, which requires multiple studies to ensure the safety of multiple sclerosis patients, especially in women during pregnancy.

Recommendations: The review recommends further research studies on changing the doses of interferon and adding some pharmaceutical compounds accompanying the use of interferon to reduce its potential effects on liver and kidney cells and sex hormone levels in M.S.patients

Keywords: Interferon- β-1a, Multiple, sclerosis, liver and, kidney, sex hormone.

1.1. Introduction:

Multiple, sclerosis (M.S) a chronic inflammatory disease affect (C.N.S) central nervous system leading damage in myelination, neuronal loss. Militated axons central nervous system are the target of attacks in MS, causing varying degrees of damage to both axons and myelin. [1] Recurrent neurological symptoms that last for a full day and are not accompanied by fever are called clinical relapses. M, S affects more Tow million from people world, wide. The disease is diagnosed between the ages of 20 to 50, with women being more susceptible to disease than men. People of Northern European and White descent They are more susceptible to disease, with the prevalence decreasing the farther away from the equator. Gender, age, race, genetics, geography, and environment are risk factors for MS. MS onset is around 24 years of age, with a female / male rate of 2 to 1. [3] mean of age to death in M, S patients is fifty-eight years, compare to a US national average of 72 years. United States, MS is more commonly in Caucasians than in African Americans. However, the typical clinical course is more severe among affected African Americans [4]. worldwide prevalenc of multiple, sclerosis ranges Five to three hundred cases of disability per 100, 000 people and increases depending on geographic location. Studies have also confirmed that the average life expectancy of patients is lower than that of the general population. Scientific research on multiple sclerosis has documented that female are more affected than male, with a ratio: of 1:3. Diagnosis of the disease is based on a combination of symptoms, clinic biochemical variables, and MRI findings.[5].

1.2. Multiple sclerosis treatment with drugs

Development of medications to treatment M.S In recent years, the production of 23 disease-modifying therapies has been recorded. [6]. The treatments used are divided into two types: the

first is the basic or first-line treatments, which are drugs with low or intermediate efficacy (LETA), (interferons, glatiramer, teriflunomide, fumarate), and the second type is the highly effective therapeutic agents (HETA) such as S.1.P receptor agonists, anti-C.D-20 monoclonal antibodies, alemtuzumab, natalizumab, and cladribin. [7] The treatment strategies of multiple sclerosis are accompanied by great concerns due undesirable effects of the medications used.This review focuses on the drug interferon beta, which is used as a basic treatment for many M.S patients, and discusses its effects on liver and kidney function and on the levels of sex hormones in the blood of patients taking this drug The effect of Betaseron®/Betaferon® as initial treatment was studied in a total of 468 multiple sclerosis patients who were divided to 2groups: group was given a dose of 250 μg of interferon beta-1b and second group was given a Patients were given a placebo Every two days for two year. The study The study found that of 468 patients initially randomized (IFN.B-1b drug 292; placebo 176), 358.0 were followed for 5- years. The 3-year analysis showed that IFNB-1b used as initial treatment, compared with later treatment, lower risk of developing chronic scleroderma syndrome (CDMS) by 37% over five years, led to a 20% reduction in the relapse rate, and a significant decline in formation of new lesions. Early treatment also reduced the incidence of EDSS by 40% (after 3 years and 24% after 5 years, respectively).[25]

1.3. Interferon β

Beta-interferons (1a, 1b) are cytokines, which are protein complexes that interact with receptors on cells to produce antiproliferative, antiviral, and intracellular immunomodulatory effects. Beta - interferon reduces symptoms of multiple sclerosis. [8]. Interferon- beta one of the most important causes of Slight liver injury, which can progress to severe liver injury accompanied by jaundice. Human interferon beta-huIFN-β is a protein Contains of 166.o amino acids, which binds to monosaccharides at a single site. [9] Interferons are a type of helical cytokine, similar to helical proteins. [10] β-Interferon is cytokine typ.1 It is produced in macrophages and fibrotic tissue in response to viral infections and antigens. Interferon beta differs from interferon alpha in chemical structure and antigen, but they act on the same cell surface receptor. Although they act on the same receptor, the interferons have different internal effects and actions. Interferon beta acts as an immunomodulator, and studies have documented its ability to alleviate and treat relapsing-remitting multiple sclerosis. It was first legally used in the United States in 1993.. Interferon beta comes in five forms:

Betaseron – β-interferon -1b (250.00 micro gram) in day subcutaneously. Introduced in 1993.

Extavia – β-interferon _1b (250.00 micro grams) in day subcutaneously. Introduced in 1993.

- Avonex - interferon beta-1a (30.00 micrograms), intramusc`ularly injected weekly. Approved in 1996.

Rebif - interferon beta-1a (8.8 micrograms, 22 micrograms, 44 micrograms) subcutaneously for three weekly doses. Approved in 2003

- Plegridy – peginterferon ß-1a, 63.0, 94.0, 125.0 mcg for 14 days. subcutaneous injection approved in 2014.

Several disease-modifying therapies for MS have been studied for their effectiveness in reducing relapses, preventing progression to relapsing-remitting M.S, and preventing the patient from becoming physically disabled. Some treatments Approved for use in patients with relapsoing-remitting M.S. The most important initial treatment for the disease is β-interferon IFN-β, approved at 1993. Among these is subcutaneous interferon beta-1a (Rebif®), approved in and Canada and Europa at 1998, and approved for M.S in U S A tates year 2002. Numerous bioclinical studies & remitting MS. Research studies on interferon β-1a have been ongoing For fifteen years, the most important clinical use of β-interferon _1a remains subcutaneous injection., particularly in pregnant and breastfeeding women. It can be considered as well for elderly patientes in whom M.S activity is declining & the Immunosuppression associated with

alternative therapies is a concern. Also, subcutaneous injections of interferon-1a are used for comparison in bioclinical studies, providing a precursor to studying the mechanics of how multiple sclerosis begins and progresses.11] Studies have shown a significant reduction in relapse in M.S patients treated by β-interferon.[12] β_Interferon _1-a (I.FN) is considered a first-line drug, with subcutaneous (SA) and intramuscular (I.M) IFN β-1a. The action of mechanism in this drug is immune-modulation.[13, 14] Interferon _1a acts to up regulate anti_inflammatory cytokines & reduce pro_inflammatory cytokine. Previous studies have confirmed safety& efficacy of β_interferon _1a, other scientific studies have demonstrated some of the many and varied side effect of β-interferon _1a in MS patients.[15-17]

1.3.1. Mechanisms of Interferon Action

Interferons are glycoprotein compounds, first discovered as cytokines with the potential to It plays an important antiviral agent in the body [18]. Development in recombinant DNA techniques to produce compounds based on α-interferon drugs as treatments for viral diseases [19]. Research has confirmed the effectiveness of interferon as a immune-modulator, and interferon-beta has begun to use as an important immune-modulatory treatment in multiple. sclerosis patients [20].

The type 1 interferon-beta Signal system plays a fundamental sharing in maintaining homeostasis, immune function. Focus has increased on interferon-beta As a treatment option for multiple, sclerosis because it has proven effective as an antiviral, immunomodulatory, and antimetastatic agent. It has also been observed that interferon-beta stimulates immune system in patients with M.S through multiple effect, most notably its effect on various immune cells [21]. Interferon beta regulates the concentrations of metallo-proteinases, interstitial cells, and Adhesion molecules, which prevents T cell adhesion to endothelial cells and the transmigration of White blood cells across the blood-brain barrier [22]. Mechanisms increase inflammation and worsen central nervous system damage. Interferon beta also reduces the total number of effector T cells, enhances regulatory T -cells, and strengthens ability to immunosuppress. Interferon beta increases the production of anti-inflammatory cytokines, plays a role at T cell presentation of antigens, increases death of memory B cells. [23, 24].

1.3.2. Side effects Interferon β on liver with MS patients

All five forms of interferon beta cause liver damage and jaundice 3 to 12 months after starting interferon beta-1 therapy, especially when dosing is done daily or more often per week compared to once per week.. Patients are usually asymptomatic and severe liver damage may develop years after treatment. Liver damage is usually not noticeable, but may cause severe jaundice or liver failure. [26] In a previous study of thirty-eight-year old woman with multiple sclerosis receiving treatment 250 micrograms of subcutaneous interferon beta, blood liver enzymes were measured, with abnormal levels recorded after 6 months of treatment and markedly elevated after 18 months. Upon discontinuation of interferon beta treatment, liver enzyme levels decreased significantly.. [27].

The results of the study on biochemical changes in follow-up 624 patients some treatment and un treatment M.S before and during treatment with β-interferon 1a at Various dosages confirmed the presence biochemical changes, especially with regard to enzymes of liver, hormones of thyroids and phospholipids. Effects of treatment were most evident in the increase in liver enzymes, thyroid anti-bodies and the decrease cholesterol in serum. These were effects mostly temporary & disappeared spontaneously without discontinuation of treatment. [28]

Christopher et al.'s study of 38 women with MS in the UK confirmed acute hepatitis at 22 μg three times weekly for 21 months. [29]. Kozielewicz and Pawlowska's study in Poland showed that IFN β-1a given a concentration of 30 μ.g in week for 4 weeks resulted severe liver failure in MS patients. [30] Duccini's study in the United States confirmed that patients developed autoimmune hepatitis when they took IFN beta-1a treatment for 24 months [31].

They developed autoimmune hepatitis when 44 Japanese men were given 7.5 μg of interferon beta for five days [32]. A study by Mishra et al. in Canada, which included 43 women with multiple sclerosis treatment with β_interferon three times a week for 3 months, reported that they developed autoimmune hepatitis (AIH).[33].Occurrence of liver dysfunction at patients with interferon beta treated in Taiwan [34].

study by Byrnes et al. in women with MS treated with 30 micrograms once weekly of IFN beta-1a showed liver damage after 10 months of treatment. [35].An Italian study on 46 cases of the women(MS patients) being treated a dose of 30 micrograms once a week for 1.5 months with IFN beta-1a suffered severe liver failure [36].Yoshida et al., a study in Canada in 59 women treated dose 22 μg three times a week for 7 weeks, reported severe liver failure [37]. Neumann et al., in Germany, confirmed the occurrence of autoimmune hepatitis in 71 men with MS after four months of treatment with β_interferon.[38]. Previous studies [39, 40, 41, 42] in different countries have confirmed that interferon beta-1 given in different doses led to Acute inflammation of the liver. In M.S patients treated by β-interferon 1a, significant elevations of alanine aminotransferase (ALT) were observed 59% of patients after six months, 64% after eleven months, and 67% after twenty-four months. More than 50% liver enzyme elevations were found within the first three months of treatment, and more than 75% within the first six months. With dose adjustments in the same patients, liver enzyme levels gradually decreased. The study also confirmed that taking β-interferon _1a treatment causes serious side effects on liver cells (hepatotoxicity) associated with interferon [43].

1.3.3. Side effects Interferon β on kidney with MS patients

Type I interferon can cause Tissue damage in renal cells, It also has a direct effect on the physiology and function of many of them, such glomeruli, cells of epithelial, and cells of endothelial. Type I interferon-associated disorders may lead to kidney dysfunction & share common pathological and histological feature, including collapsed glomerulopathy, proliferation of parietal epithelial cells, and can also be induced by treatment with recombinant interferon with other chemicals. Some diseases that affect the kidney, for example, thrombotic microangiopathy and vasculitis.[44]. Hansen et.al in a UK research recorded that MS patients treated 22 mcg 3 times weekly for one year with interferon beta-1a had. Systemic lupus erythematosus, Systemic lupus erythematosus, Vasculitis: Thrombotic microangiopathy and acute kidney injury (45)

A previous study conducted United States on 41 patients suffer multiple sclerosis who received (β-interferon 1a)at a conc. of 44 micrograms three times a weekly for 4 month confirmed that they had FSGS Focal segmental glomerulosclerosis [46]. Previous studies [47, 48] have also confirmed that MS patients who received different doses and for different durations of interferon beta-1a experienced serious kidney side effects (FSGS).Capobianco et al. reported that some M.S patients treatment by β-interferon -1b developed glomerulonephritis and sarcoidosis-like lung disease [49].Previous studies conducted in different countries have confirmed that receiving repeated doses and long periods of IFN beta-1a leads to thrombotic microangiopathy (TMA)[50, 51, 52, 53].OtY and Saleh's study in the United Arab Emirates, which included 28 men with multiple sclerosis who received interferon beta-1 once weekly for two years, also reported nephrotic syndrome. [54].

1.3.4. Side effects Interferon β on sex hormones with MS patients

Multiple sclerosis (MS) More common in women than in men [55]. Incidence of M.S among women has increasing significantly over past century. Several studies have confirmed a real increase in MS among women. Women are also more affected by relapses during treatment than men, but there are no statistically significant differences. Furthermore, no differential effects of interferon beta have been established between men and women. [56-58]

Multiple sclerosis It is less common in men than women., this increase increases over time. Sex has a significant role and function in MS and increased incidence of relapses. Must be taken into

consideration when developing, designing and producing medicines. for this disease, and in ongoing clinical research to determine impact of gender on mechanisms of MS treatment. This review discusses the most important side effects observed in previous studies of interferon's used to treat M.S, including effects on liver, kidneys, and some sex hormones.. Bove et al. observed decreased Testosterone levels measured in male and female patients compared to healthy individuals of the same age [59]. Previous studies have reported testosterone, as a therapeutic, has a direct effect on nervous system [60, 61]. Another research paper evaluating the effects of testosterone therapy on gray matter volume in MS patients [61] recorded hormone of testosterone treatment prevented gray matter loss, results a significant increase in volume of the right prefrontal cortex [62].. another study tested blood samples from multiple, sclerosis patients, measuring cytokine & growth factor levels and number PBMCs [62]. Results also noted that testosterone treatment cause a change in composition of peripheral lymphocytes, a decrease in T-cells and a increase in natural killer cell, in addition to a significant decrease in the production of interleukin-2 from peripheral blood cells, while an increase in the production of growth factor (TGF-β1). The study concluded that testosterone treatment multiple sclerosis patients has an immune-modulatory effect [63].

According to recent studies, the risk of developing MS in women is three times higher than in men. However, male are more likely to develop severe M.S and early [64, 65]. The disease develops faster in men when it is diagnosed at older age 30 [55]. Multiple sclerosis begins early in women and have a higher number of relapses than men [66, 67]. Recovery after relapse is poorer in men than in women [57].Interferon beta (IFN-β) No association has been observed with increased rates of spontaneous abortion or fetal complications. However, to avoid risks during pregnancy, the risks of taking oral contraceptives with interferon beta therapy should be monitored. [68]. The results of the study, which was conducted on 542 pregnancies resulting in 466 live births and followed up for four years of life, Exposure to β-interferon treatments in pregnancy state, breastfeeding did not have No negative effects on the development of child in womb and its development during the study period [69]. Pregnancy and childbirth are issues of concern for many women patients. Effective disease-modifying therapies have been well controlled in recent decades, and several studies The investigation has been carried out Effects of disease modifying treatments on pregnancy.[70, 71] Recent studies in a group of mild M.S patients have shown that relapses were 30% less severe in study group and may not exceed pre-pregnancy levels. Clinical studies also suggest that breastfeeding has a protective effect against postpartum relapses.[72, 73] Two studies were conducted year 2022, for more than 81 patients were treated β-interferon _1a, &more than 627 patients were treated intramuscular (IM) β-interferon -1a, based on clinical trials. Both studies provided important data on women of childbearing age with M.S exposed to interferon. results showed that 2447 potential pregnancies with 948 The incidence of spontaneous abortions was 10.7%, and incidence of live births with congenital anomalies was 1.8%, which is roughly comparable to reported incidence of 21% spontaneous abortions and 2.1–4.1% congenital anomalies [74, 75]. The results of a study conducted in two Nordic countries, Finland and Sweden, which included 2.831 pregnancies, found no significant adverse effects in pregnant women and infants exposed to interferon beta before, during, and after pregnancy compared to women not exposed to disease-modifying drugs [76]. In a study of 12 patients taking disease modifying medication for M.S before pregnancy, four cases showed no significant differences statically in relapse rates and E.D.S.S before, during, after delivery compared to the healthy group. The study showed that there were no significant differences in obstetric outcomes. M.S group had significantly higher rates of assisted reproductive treatment and lower rates of breastfeeding, both of which were a significant. [77] There is a significant decrease in the rate of relapses and complications of the disease during pregnancy, but it tends to increase after childbirth, [78] and relapses decrease after menopause.[79] Hormonal factors are factors influencing the development of disability, [80] Multiple sclerosis (MS) occurs at an early age in men and during the premenopausal period in women. [81, 82] MS is an inflammatory disease that is more prevalent in women, but recent

observations suggest that the sex ratio may be increasing due to the increased incidence among women over the past century. [83] Statistical studies indicate that the sex ratio in many countries is steadily increasing, such as Canada, where the sex ratio increased from 1.9 to 3.2, and Sweden from 1.7 to 2.7 for patients born in the 1930s compared to the 1980s. [84] No regional differences in the sex ratio have been observed in New Zealand.. [85] The incidence of MS may vary by geographic location. [86] In recent years, the sex ratio at onset of MS in Ontario, Canada, was stable from 1996 to 2013. [87] The increased incidence is likely to be a sex interaction and environmental factors. Some researchers attribute the observed increase in MS among women to environmental changes and numerous lifestyle changes in recent years, including delayed age of first pregnancy, use of hormonal and non-hormonal contraceptives, increased rates of smoking, and long working hours. The increased susceptibility of women to MS is due to several factors, including hormonal, genetic, and environmental factors. [88, 89] Sex hormones play an important functional role in the risk of developing MS and the progression of the disease. Changes in sex hormone levels affect most bio clinical and radiological variables and factors related to disability. Sex chromosomes also play an important role in sex differences in MS risk and disease progression. [90] Puberty, pregnancy, and menopause are periods in women when sex hormone levels change significantly, and puberty is a risk factor for MS. Studies have shown a significant statistical association between early puberty and increased MS complications and the onset of severe disease symptoms at an earlier age in women. [91, 92] In MS in young men and women, studies have shown that girls experience symptoms more frequently at puberty, due to the stimulation of the immune system by sex steroid hormones during puberty. [93, 94] Non-pregnant women are More susceptible to multiple sclerosis than who have had multipl, pregnancies.[95] Previous studies have shown that estrogen has a biphasic dose-response effect, stimulating the immune system at Low levels in conjunction with the menstrual cycle, while suppressing immunity at high concentrations during pregnancy.[96, 97]

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