Examination of the scientific evidences for off-label use of medications in non-alcoholic fatty liver disease

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Abstract
Introduction: non-alcoholic fatty liver disease (NAFLD) is considered to be a representation in the liver of insulin resistance or metabolic syndrome, and is a common cause of chronic hepatitis, which can lead to cirrhosis and hepatocellular carcinoma. Currently, there are no pharmacologic therapies approved by the U.S. Food and Drug Administration (FDA) and National Health Surveillance Agency of Brazil (ANVISA) for the NAFLD treatment. Objective: the aim of this study is to assess the evidences for off-label use of medication in NAFLD. Methodology: a systematic search was made in MEDLINE-PubMed for papers published between January 1990 and December 2017, addressing the off-label use or unlicensed drugs for NAFLD treatment. An integrative review was conducted and the data analyzed thematically. Results: of the 3540 studies retrieved, 50 met the inclusion criteria by to contain information about the off-label prescriptions in NAFLD. In this integrative review of the published literature, off-label treatment of NAFLD was generally associated with good short-term and long term outcomes. Conclusions: after analyzing the data, may conclude that literature includes studies that provides scientific evidence for the off-label drugs use in NAFLD. The evidence of the evaluated studies, suggest that metformin treatment has best effect on reducing hepatocyte fat deposition with regard to other drugs evaluated. However, randomized, placebo controlled studies should be performed to confirm this evidence.

Keywords: Off-label use. Fatty Liver. Drug Therapy. Non-Alcoholic Fatty Liver Disease.

Resumo
Introdução: hepatopatia gordurosa não alcoólica (DHGNA) é considerada uma representação da resistência insuliníca ou síndrome metabólica no fígado, sendo uma causa comum de hepatite crônica, podendo levar à cirrose e carcinoma hepatocelular. Atualmente não existem medicamentos aprovados pelo FDA (Food and Drug Administration) e pela Agência Nacional de Vigilância Sanitária do Brasil (ANVISA) para o tratamento DHGNA. Objetivo: o objetivo deste estudo é avaliar as evidências para o uso off-label de medicamentos em DHGNA. Metodologia: a pesquisa foi realizada no MEDLINE-PubMed com artigos publicados entre janeiro de 1990 e dezembro de 2017, abordando o uso off-label ou drogas não autorizadas para tratamento da DHGNA. Uma revisão integrativa foi realizada e os dados analisados tematicamente. Resultados: dos 3540 estudos encontrados, 50 preencheram os critérios de inclusão por conter informações sobre o uso off-label em DHGNA. Nesta revisão integrativa da literatura, os tratamentos off-label da DHGNA foram geralmente associados a bons resultados a curto e longo prazo. Conclusões: após a análise dos dados, pode-se concluir que a literatura inclui estudos que fornecem certas evidências científicas para o uso off-label de drogas na DHGNA. As evidências dos estudos avaliados sugerem que o tratamento com metformina tem melhor efeito na redução da deposição de gordura dos hepatócitos em relação a outros medicamentos avaliados. Entretanto, estudos randomizados e placebos controlados devem ser realizados para confirmar essas evidências.

Palavras-chave: Uso off-label. Fígado Gorduroso. Tratamento Farmacológico. Hepatopatia Gordurosa não Alcoólica.
there a violation of ethical guidelines or other security regulations. However, off-label use out dare the authority of the medicines regulatory agencies, discouraging the development of research of pharmaceutical industries and conducting trials for new drugs or new indications.

Several studies have shown that this is a common practice in various health care settings, and studies demonstrated that off-label use may account for about 20% of prescriptions in the United States.

Non-alcoholic fatty liver disease (NAFLD) it has been considered a mimicry in the liver of insulin resistance (IR) or metabolic syndrome, and is a common cause of chronic hepatitis, which can progress to cirrhosis and hepatocellular carcinoma.

Individual carriers of NAFLD it has the risk of developing progressive hepatic disease necessitating of efficient treatment alternatives. However, despite decades of clinical trials, no single on-label treatment has been recommended for all patients with NAFLD. Therefore, the NAFLD therapy is extremely sparse, and off-label therapies make up the treatment paradigm. Estimates of off-label sales in 2012 for NAFLD to be approximately $233 million across the United State and five major European markets of France, Germany, Italy, Spain, and the United Kingdom, and the demand for off-label pharmaceuticals for NAFLD is expected to grow to US$1.36 billion by 2017.

In this article we report the studies available in the literature on NAFLD treatment, through an integrative bibliographical review, with the objective to support the off-label use of medications in NAFLD.

METHODOLOGY

An integrative review was made by searching the Medline-Pubmed international database for view of manuscripts. The Medline-Pubmed is taken to be a of the largest medical literature databases in the world. The MeSH (Medical Subject Heading) was the used descriptor for Medline. The keywords produced results specific to documents using the terms which are described below.

Whittemore and Knafl’s methodology for integrative reviews guided the data extraction and subsequent analysis. Studies meeting the review inclusion criteria were analyzed sequentially. Data were extracted and organized under the following headings: year, study purpose and design, sample size, study variables, study findings and limitations. Articles were graded using a commonly accepted categorization scheme, which is recommended for grading the quality of evidence published in the medical literature.

The selection of these databases was based on the wide range of medical journals covered by each of them and our goal was to provide an overview of scientific productions devoted to the topic over the time frame under analysis. The following inclusion criteria were considered during the review: articles published between January 1990 and December 2017; use of the keywords “non-alcoholic fatty liver disease”[MeSH Terms] OR “non-alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields] OR “non-alcoholic fatty liver disease”[All Fields] OR (“non”[All Fields] AND “alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non-alcoholic fatty liver disease”[All Fields] AND (“therapy”[Subheading] OR “off-label therapy”[All Fields] OR “off-label treatment”[All Fields] OR “off-label therapeutics”[MeSH Terms] OR “off-label therapeutics”[All Fields] AND (“1990/01/01”[PDAT]: “2017/12/31”[PDAT]). Only studies with abstract in English were selected.

The following exclusion criteria were considered during the review: Animal studies, experience reports, abstracts published in proceedings, reviews, and editorials.

The authors of the cited articles declare no conflicts of interest regarding the choice of those drugs, and equally the authors this manuscript have no conflicts of interests to declare and have received no financial or material support related to the same.

RESULTS

The search strategy identified 3540 unique publications regarding NAFLD. Of the 3540 scientific productions identified, 50 studies were selected by contain information about the off-label treatment of NAFLD, aimed at the underlying mechanisms of injury, and were excluded articles for one or more of the following reasons: duplicates, review bibliographies, and by the title/abstract review. The articles selection process is depicted in Figure 1.
Fifty studies were selected by contain information about the off-label treatment of NAFLD (Table 1).

Table 1 – Off-label agents for treatment of NAFLD.

| DRUG CLASS                  | DRUG                                      | REFERENCES |
|-----------------------------|-------------------------------------------|------------|
| ANTI-OBESITY MEDICATION     | Orlistat                                  | 9, 10      |
|                             | Sibutramine                               | 11         |
| INSULIN SENSITIZING         | Pioglitazone                              | 13, 14, 15 |
|                             | Metformin                                 | 17, 18, 19, 20 |
| LIPID LOWERING              | Statin                                    | 24, 25, 26, 27 |
|                             | Fibrates                                  | 29, 30, 31 |
|                             | Omega-3 fatty acids                       | 32, 34     |
|                             | Ezetimibe                                  | 35         |
| ANTIOXIDANTS                | Vitamin E                                 | 37, 38, 39, 40, 41, 57 |
|                             | Betaine                                   | 43, 44, 45, 47 |
|                             | N-Acetyl-cysteine                         | 49         |
|                             | Silymarin                                  | 53, 54, 55 |
| ANTI-TUMOR NECROSIS FACTOR | Pentoxifylline                            | 61, 62, 63 |
| PROBIOTICS                  | VSL#3                                     | 66, 67     |
| CYTOPROTECTIVE              | Ursodeoxycholic acid                      | 69, 70, 71 |
| NOVEL TREATMENTS            | Renin-Angiotensin System blockers         | 74, 75     |
|                             | Oligofructose                             | 77         |
|                             | Incretin Modulators                        | 79, 80     |
|                             | Second generation sulfonylureas           | 81         |

Source: Medline-Pubmed

The summary of the included studies and related outcomes is shown in Table 2.

Table 2 – Summary of the included studies

| Author                      | Year  | Design/Sample Size | Age   | Intervention                  | Duration | Control arm                     |
|-----------------------------|-------|--------------------|-------|-------------------------------|----------|---------------------------------|
| Corrado, Torres e Harrison. | 2014  | Comparative/50     | Adult | Orlistat                      | 36 weeks | Vitamin E                       |
| Zelber-Sagi et al.          | 2006  | double-blind/52    | Adult | Orlistat                      | 26 weeks | Placebo                         |
| Sabuncu et al.              | 2003  | Comparative/25     | Adult | Sibutramine                   | 26 weeks | Orlistat                        |
| Shadid e Jensen             | 2003  | Prospective /20    | Adult | Pioglitazone                  | 18 weeks | --                              |
| Promrat et al.              | 2004  | Prospective/18     | Adult | Pioglitazone                  | 48 weeks | --                              |
| Aithal et al.               | 2008  | Comparative/73     | Adult | Pioglitazone                  | 52 weeks | Placebo                         |
| Resuli et al.               | 2012  | Comparative/61     | Adult | Metformin                     | 24 week  | Low fat diet                    |
| Loomba et al.               | 2009  | Prospective/28     | Adult | Metformin                     | 48 weeks | --                              |
| Schwimmer et al.            | 2005  | Open-label/10      | Children | Metformin                | 24 weeks | --                              |
| Marchesini et al.           | 2001  | Comparative/26     | Adult | Metformin                     | 16 weeks | Without treatment               |
| Kimura et al.               | 2010  | Open-label/43      | Adult | Atorvastatin                  | 52 weeks | --                              |
| Kargiotsi et al.            | 2015  | Prospective/20     | Adult | Rosuvastatin                  | 52 weeks | --                              |
| Hygo et al.                 | 2011  | Prospective/13     | Adult | Pitavastatin                  | 52 weeks | --                              |
| Nelson et al.               | 2009  | Double-blinded/60  | Adult | Simvastatin                   | 52 weeks | Placebo                         |
| Fernández-Miranda et al.    | 2008  | Prospective/60     | Adult | Fenofibrate                   | 48 weeks | --                              |
| Basaranoglu et al.          | 1999  | Controlled trial /46 | Adult | Gemfibrozil                   | 4 weeks  | Without treatment               |
| Ogawa et al.                | 2003  | Prospective/6      | Adult | Bezafibrate                   | 5 years  | --                              |
| Masterton et al.            | 2015  | Double-blind/50    | Adult | Omega-3                       | 26 weeks | Placebo                         |
| Nogueira et al.             | 2016  | Double-blind/50    | Adult | Omega-3                       | 26 weeks | Placebo                         |
| Nakade et al.               | 2017  | Meta-analysis/27   | Adult | Ezetimibe                      | --       | --                              |
| Chalasani et al.            | 2009  | Double – blind/247 | Adult | Pioglitazone or vitamin E    | 2 years  | Placebo                         |
| Nobili et al.               | 2006  | Double – blind/90  | Children | Vitamin E                | 52 weeks | Placebo/ Vitamin C             |
| Arani et al.                | 2014  | Clinical Trial/119 | Children | Pioglitazone and Metformin    | 16 weeks | --                              |
| Miglio et al.               | 2000  | Double-blind/191   | Adult  | Betaine                       | 8 weeks  | Placebo                         |
Currently treatment is just with off-label drugs. The NAFLD is hepatic parenchymal lesion not caused by excessive consumption of alcohol, including by the sequence simplex fatty liver, steatohepatitis, greasy hepatic fibrosis and cirrhosis. It common hepatic disorders in contemporary society, mainly due to the increase numbers of overweight and obese individuals worldwide. The pathogenesis of NAFLD it seems to be related to IR syndrome and oxidative stress, and until the moment, no effective drug was obtained for treatment of NAFLD.

No pharmacological drug it was further approved for the treatment of NAFLD, despite of several clinical trials. Currently treatment is just with off-label drugs. In this study, we revised research studies that provide evidence for off-label use of medications in NAFLD, with the goal of providing an overview of scientific productions devoted to the topic selected in medical journals made by searching the Medline-Pubmed international database that was utilized to be a of the largest medical literature databases in the world. Although it has been possible to identify useful findings from this review, there are important limitations, especially when applying these findings to clinical practice. The content of these studies, in highly selected populations, is presented below through detailed analysis.

### DISCUSSION

The main findings of this integrative review provide scientific evidence for the off-label drugs use in NAFLD. The NAFLD is hepatic parenchymal lesion not caused by excessive consumption of alcohol, including by the se-quence simplex fatty liver, steatohepatitis, greasy hepatic fibrosis and cirrhosis. It common hepatic disorders in contemporary society, mainly due to the increase numbers of overweight and obese individuals worldwide. The pathogenesis of NAFLD it seems to be related to IR syndrome and oxidative stress, and until the moment, no effective drug was obtained for treatment of NAFLD.

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| Author                  | Year | Design/Sample Size | Age | Intervention                              | Duration | Control arm     |
|-------------------------|------|--------------------|-----|-------------------------------------------|----------|-----------------|
| Abdelmalek et al.       | 2001 | Prospective/10     | Adult | Betaine                                  | 52 weeks | --              |
| Mukherjee et al.        | 2014 | Prospective/35     | Adult | Betaine                                  | 3 years  | --              |
| Abdelmalek et al.       | 2009 | Placebo-control/55 | Adult | Betaine                                  | 52 weeks | Placebo         |
| Khoshsbaten et al.      | 2010 | Prospective/30     | Adult | N-acetylcysteine or vitamin C             | 52 weeks | --              |
| Solhi et al.            | 2014 | Case/control/64    | Adult | Silymarin                                 | 8 weeks  | Placebo         |
| Cacciapuoti et al.      | 2013 | Prospective/72     | Adult | Silymarin                                 | 12 weeks | --              |
| Aller et al.            | 2015 | Case/control/36    | Adult | Silymarin plus vitamin E                  | 12 weeks | Hypocaloric diet|
| Erhardt et al.          | 2011 | Case/control/97    | Adult | Vitamin E or multivitamin supplements     | 52 weeks | Healthy controls|
| Karim et al.            | 2016 | Quasi experimental | Adult | Pioglitazone                              | 12 weeks | Pentoxifylline  |
| Zein et al.             | 2012 | Double-blind/55    | Adult | Pentoxifylline                           | 3 years  | Placebo         |
| Van Wagner et al.       | 2011 | Case/control/30    | Adult | Pentoxifylline                           | 52 weeks | Placebo         |
| Wong et al.             | 2013 | Case/control/20    | Adult | Probiotics                               | 26 weeks | Placebo         |
| Alisi et al.            | 2014 | Double-blind/48    | Children VSL#3 |                                            | 16 weeks | Placebo         |
| Parikh et al.           | 2016 | Open-label/250     | Adult | Vitamin E                                 | 52 weeks | Ursodeoxycholic acid |
| Pietu et al.            | 2012 | Prospective/101    | Adult | Ursodeoxycholic acid with vitamin E      | 11 years | --              |
| Troisi et al.           | 2013 | Case-control/87    | Elderly | Ursodeoxycholic acid                     | 26 weeks | Diet            |
| Yokohama et al.         | 2004 | Prospective/70     | Adult | Losartan                                 | 48 weeks | --              |
| Georgescu et al.        | 2009 | Comparative/54     | Adult | Valsartan                                | 80 weeks | Telmisartan     |
| Daubioul et al.         | 2005 | Double-blind/28    | Adult | Oligofructose                            | 8 weeks  | Maltodextrine   |
| Fukuhara et al.         | 2014 | Prospective/44     | Adult | Sitagliptin                              | 52 weeks | --              |
| Ohiki et al.            | 2012 | Comparative/82     | Adult | Liraglutide                              | 8 years  | Sitagliptin     |
| Morita et al.           | 2005 | Case/control/10    | Adult | Nateglinide                              | 20 weeks | Non-treated     |

Source: Own Authorship

### ANTI-OBESITY MEDICATION

**Orlistat and Sibutramine**

Orlistat enteric lipase inhibitor which reduces dietary fat absorption and sibutramine a serotonin and norepi-nephine reuptake inhibitor that increase satiety, its med-ications used on-label for weight loss, and studies have examined the effects of these medications on NAFLD.  

Zelber-Sagi et al.\(^9\) assessed the effect of orlistat in patients with NAFLD. In randomized, double-blind, placebo-controlled study, 52 individuals with diagnosis by ultrasound (US) of NAFLD were randomized to receive either orlistat a dose of 120 mg 3 times daily for 6 months or placebo, besides participating of an identical behavioral weight loss program. The study participants were evaluated monthly by abdominal US, lipid and liver enzyme profiles, insulin levels, as well as monitoring of anthropometric parameters, and nutritional follow-up. At the beginning of the study 40 individuals NAFLD present confirmed by hepatic biopsy, will 22 underwent a second hepatic biopsy at the end of the study. The results do study showed that the orlistat use improves liver enzyme profiles and standard US hepatic in individuals with NAFLD, as well as the weight reduction\(^9\).

Sabuncu et al.\(^11\) investigated the effects of pharmaco-logical anti-obesity therapy on the findings of NAFLD, in which evaluated 2 groups, a group with 13 individuals in
the sibutramine group and 12 individuals in orlistat group. The evaluation of obese subjects with NAFLD consisted of the use of sibutramine or orlistat for 6 months, and low caloric diet. Hepatic enzyme profiles, IR evaluation and hepatic US pattern were assessed at baseline and after 6 months of study. The results of study showed that both sibutramine and orlistat induced the weight losses that resulted in reduction of IR, improvements in hepatic biochemical profiles and US pattern of NAFLD11.

Corrado, Torres e Harrison9 carried out a study to determine if an association of orlistat with caloric restriction diet in overweight individuals with NAFLD, would results in weight loss and improve hepatic histology. Were evaluated 50 individuals with overweight or obese, and with liver biopsy-proven NAFLD. The sample was randomized to receive a 1,400 Kcal/day diet versus 800IU of vitamin E daily, associate or not to 120 mg three times a day of orlistat by 36 weeks. The study showed that weight loss of > 9% improved the liver enzyme profiles and liver histology regardless of use of orlistat6.

• INSULIN SENSITIZING AGENTS

Pioglitazone

Acting as the high-affinity agonist of peroxisome proliferator activated receptor gamma (PPAR-γ), the pioglitazone can enhance the tissue sensitivity to insulin. Pioglitazone activates nuclear PPAR-γ, which leads to increased transcription of genes encoding various proteins regulating glucose and lipid metabolisms12.

Shadid and Jensen evaluated the changes of hepatic function in 20 volunteers carrier NAFLD treated with 30 mg pioglitazone per day for 18 +/- 0.4 weeks, as part of a study of its effects on fatty acid metabolism were performed. The study evaluated the body composition, lipid profiles and IR at baseline and after pioglitazone treatment. The results in this study showed that liver function improved in obese volunteers with NAFLD during pioglitazone treatment. However, the authors call attention that the result of study does not prove a cause and effect relationship between pioglitazone treatment and improvement of liver enzyme profiles13.

Promrat et al.14 in prospective study with 18 non-diabetic subjects with biopsy-proven NAFLD evaluated the role of pioglitazone in the treatment of NAFLD. In the study were analyzed IR, body composition and hepatic biopsy before and at the end of treatment. The subjects were treated with 30 mg daily pioglitazone for 48 weeks. The results demonstrated normalization of liver enzyme profiles in 72% of the sample, reduction of volume and hepatic fat content analyzed by magnetic resonance imaging (MRI), uniform improvement of IR and free fatty acid, and histological improvement in two-thirds of evaluated subjects. Thus, a study showed that pioglitazone use can improve as well as support the role of IR in the pathogenesis of NAFLD14.

Aithal et al.15 evaluated the pioglitazone use by 12 months in the treatment of 74 non-diabetic patients with biopsy-proven NAFLD. Were used 30 mg/day of pioglitazone or placebo, besides exercise and a standard diet. Sixty-one patients performed liver biopsies at the end of the study that demonstrated notable improvement in liver injury and fibrosis, as well as in metabolic parameters15.

Metformin

Metformin is a biguanide, on-label used as a hypoglycemic therapy in patients with type 2 diabetes mellitus, because improves sensitivity to insulin by reducing hepatic glucose production, reducing lipolysis in adipose tissue, increasing peripheral glucose uptake by the liver, skeletal muscle and adipose tissue, and inhibiting intestinal glucose absorption16.

Resul et al.17 in a study of 24 week prospective controlled trial evaluated the efficacy of metformin compared with a low fat diet (LFD) in patients with NAFLD and/or nonalcoholic steatohepatitis (NASH). The authors evaluated 61 outpatients with IR, liver enzyme profiles changed and US evidence of fatty liver. There was a significant improvement in the evaluated parameters of the patients with NAFLD and/or NASH treated with metformin plus LFD when compared with patients treated with LFD alone17.

Loomba et al.18 evaluated the improvement in the histological NASH grade with the use of 2000 mg/day metformin during 48 weeks, evaluating the metabolic profile, MRI and liver biopsy was performed in 28 patients before and at the end of the study. The results demonstrated that in 8 patients occurred a satisfactory histological response associates to improvements liver enzyme parameters. The authors of study concluded that the metformin use leads to improvements of NASH, and attribute this improvement to weight loss associated18.

Schwimmer et al.19 in a single-arm open-label pilot study for evaluate the markers of liver disease in pediatric NAFLD studied 10 non-diabetic obese children with biopsy-proven NAFLD, that were treated with metformin 500 mg twice daily for 24 weeks. The results showed improved significantly of liver enzyme profiles, liver fat, IR and quality of life in analyzed sample. However, the authors suggest the need for achievement of other large randomized-controlled trials the efficacy of metformin in children with NAFLD19.

Marchesini et al.20 conducted a study in which were treated 20 subjects with NAFLD during 4 months with 500 mg three times a day of metformin, showed an improved significantly of IR, of liver enzyme profiles, and hepatic volume reduction20.

• LIPID LOWERING AGENTS

Statins

For many patients with NAFLD are prescribed statin. The statin is a lipid-lowering agent (3-hydroxy 3-methylglutaryl-coenzyme A reductase inhibitor) used primarily
for the prevention of atherosclerosis and cardiovascular disease. Initially, concern there were that the use of statins in patients with NAFLD could potentially worsen hepatic steatosis in function of statins induce the expression of transcription factor sterol response regulatory element-binding protein-2, as well as inhibit cholesterol synthesis, leading to enhanced expression of hepatic LDL receptors and increased LDL-c uptake. However, studies showed that statin use was not associated with a higher frequency of hepatic steatosis or serum liver enzymes abnormalities, even among those with NAFLD.

Advanced glycation endproducts (AGEs) has been used with as a clinical biomarker for the attenuation of NASH, and Kimura et al. conducted a study with 43 dyslipidemic patients and biopsy-proven NAFLD to investigate whether if the treatment of NAFLD with dyslipidemia could decrease serum levels of AGEs. This study, the patients during the open-label study were treated with 10 mg daily of atorvastatin for 12 months. Fifty percent of patients performed liver biopsy, and were analyzed clinical laboratory tests, liver density by computerized tomography (CT) and oral glucose tolerance test before and at the end of the study. The study demonstrated that atorvastatin use significantly improved the metabolic parameters, serum glyceroldehyde-derived AGEs levels, and the NAFLD activity score.

The rosuvastatin effect as was also investigated in NAFLD by Kargiotis et al. in a prospective study in 20 subjects with biopsy-proven NAFLD associated with dyslipidemia and metabolic syndrome. Were analyzed hepatic US liver enzymes profile, serum glucose, serum creatinine, serum uric acid, high sensitivity C reactive protein and lipid profile were assessed before and every 3 months of treatment with 10mg by day of rosuvastatin for 12 months. The results demonstrated improved significantly of biochemical parameters, complete resolution of NAFLD in US as well as in liver biopsy. Thus, rosuvastatin use in monotherapy could ameliorate biopsy-proven NAFLD.

Hyogo et al. in a multicentric prospective study assessed the efficacy of pitavastatin therapy in NAFLD patients with dyslipidemia in 20 patients with biopsy-proven NAFLD. The subjects were treated with pitavastatin 2 mg/day during 12 months. The histological and metabolic parameters were comparatively evaluated before and at the end of treatment. The liver enzymes and lipid profiles were significantly improved, as well as the NAFLD in patients with hyperlipoproteinemia type IIB. However, in 3 patients have progression of fibrosis in course of the treatment.

Resul et al. in letter to the Editor in Atherosclerosis journal was reported a study with five patients with liver enzymes profile changed and biopsy-proven NAFLD, were treated with 20 mg of pravastatin daily for 6 months. The preliminary results showed an improvement in the histological findings of NAFLD.

A double-blinded randomized placebo-controlled trial with statin and placebo was performed to assess the utility of simvastatin therapy in NAFLD was performed by Nelson et al. The sample with 16 patients with biopsy-proven NASH making use of simvastatin during 12-month period, and analyzing the liver enzymes profile and repeating liver biopsy to assess for improvement. The results were no statistically significant improvement in histological and liver enzymes profile in simvastatin and placebo groups, demonstrated that simvastatin therapy does not seem to be an effective therapy for NAFLD.

Fibrates

The fibrates are substantiated chemically on phenylethyl acetic acid, and may improve insulin sensitivity by limiting the lipid build-up in diver tissues, including the hepatic and muscle tissue. Thus, improvement in liver function tests associated with fibrates may be due to improving these risk factors, and considering its actions it could be assumed that fibrates is useful for prevention and accompaniment of NAFLD.

Few clinical studies assessed the effect of fenofibrate on biochemical and imaging surrogates of NAFLD. Fernández-Miranda et al. studied 16 subjects and evaluated the effects of fenofibrate on the metabolic parameters, histological and clinical in biopsy-confirmed NAFLD treated for 48 weeks with 200mg/day of fenofibrate. The follow-up was done every 3 months by biochemical and clinical evaluation, and hepatic biopsy was performed at the end of the study. The results demonstrated a significant improvement of liver enzymes and metabolic profiles. However, the NAFLD score did not modified significantly. Thus, this study showed that treatment with fenofibrate in NAFLD presents effects minimal on hepatic histology.

Basaranoglu, Acbay and Sonsuz in a controlled trial studied prospectively 46 patients with NAFLD who had persistently elevated ALT. In this study two groups were evaluated, a used group gemfibrozil 600 mg/day orally for 4 weeks and other control group without treatment. The results demonstrated that group gemfibrozil improved enzymes liver profile in 74% of NAFLD patients compared with 30% of untreated control subjects. In this study no available histologic data.

Ogawa et al. in a study showed thirty-three percent of the breast cancer patients who underwent tamoxifen treatment were diagnosed NAFLD, and to these patients were administered bezafibrate with the purpose of preventing progression to hepatic cirrhosis. In this study, the bezafibrate use showed improvement of follow-up image findings of patients with biopsy-proven NAFLD. Thus, the authors conclude that the NAFLD could be prevented with bezafibrate use in patients treated with tamoxifen without the need of interrupting.

Omega-3 fatty acids

Omega-3 fatty acids belong to a family of polyunsaturated fatty acids and have beneficial effects on metabolism and inflammation. However, studies for test the effects of omega-3 fatty acids in NAFLD are contradictories.
placebo-controlled, evaluated 50 patients to check the effect of omega-3 fatty acids in patients with NAFLD. The patients were randomized in two groups, with the use of 4 grams daily of omega-3 fatty acids or placebo during six months. The study had as primary endpoint the evaluation of the modification ultrasound grade of NAFLD and how secondary endpoints included change in enzymes liver profile and quality of life using the WHO-QOL-BREF score. The results of this study showed there was no significant difference between omega-3 fatty acids group and placebo in primary endpoint and secondary endpoints, contraindicating the use of omega-3 fatty acids as a treatment for NAFLD.

However, Nogueira et al. evaluated the effects of supplementation with received three capsules daily, each containing 0.315 g of omega-3 polyunsaturated fatty acids in patients with liver biopsy-proven NAFLD, and showed significantly improvement on liver histology and in the plasma lipid profile of analyzed sample.

**Ezetimibe**

Ezetimibe is a potent inhibitor of cholesterol absorption, and the studies analyzed in treating of NAFLD presented variable results. Nakade et al. in a meta-analysis to evaluate the efficacy of ezetimibe in treating NAFLD demonstrated that only in a few studies the ezetimibe attenuates serum liver enzymes and improvement hepatocyte ballooning, suggesting that larger studies and more randomized placebo-controlled trials are necessary to determine their effectiveness on NAFLD.

**Vitamin E**

Vitamin E, by virtue of being an antioxidant, has been shown to be effective in reducing raised transaminases in a significant proportion of patients with NAFLD. Thus, Vitamin E is recommended for patients with a histological diagnosis of NAFLD. Vitamin E can cause adverse effects that should be monitored while in use.

A retrospective study for evaluated the long-term efficacy of treatment with Vitamin E in 17 patients with biopsy-proven NAFLD for more than two years with a dose of 300 mg/day, compared two group (patients with and without fibrosis regression), demonstrated significant improvement of liver enzymes profile, IR and hepatic fibrosis markers was performed by Chalasani et al. Thus, this study showed that prolonged periods treatment with Vitamin E it can be expected an improvement NAFLD fibrosis degree.

In the PIVENS study, a randomized, multicenter, double-masked, placebo controlled trial with pioglitazone or vitamin E improves hepatic histology in non-diabetic adults with NAFLD compared to treatment with placebo were reevaluated the associations between modifications in liver enzymes profile, body weight and hepatic histology. The reassessment showed that Vitamin E use can significantly improve the liver enzymes profile and liver histology independently of weight loss.

Nobili et al. conducted a 12-month double-blind placebo study for evaluate the effect of Vitamin E on liver enzymes profile and IR in children with biopsy-proven NAFLD it includes 90 children who used a diet with 25-30 cal/kg/d, physical exercises, and placebo or Vitamin E 600 IU/day plus Vitamin C 500 mg/day. At the end of the study was observed that a balanced calorie diet and physical exercise in NAFLD children it seems to induce to a significant improvement of liver enzymes profile and IR, than Vitamin E and Vitamin C therapy.

Another study was performed by Arani et al. with obese children evaluated the effect of Vitamin E and metformin on NAFLD based on sonographic. An interventional study by four months including 119 children with body mass index (BMI) over 95th percentile were divided into four treatment groups: the first group received Vitamin E 400 IU/day, the second group received Vitamin E 800 IU/day, the third group children age < 12 years received metformin 1gr/day, and the forth group children age > 12 years received metformin 1.5 gr/day. Based on the results obtained, the authors concluded that both Vitamin E 400 IU/day and metformin 1.5gr/day are efficacious in NAFLD treatment in obese children based on sonographic findings.

**Betaine**

Betaine is the trimethyl derivative of glycine present in human plasma due to dietary intake and endogenous synthesis in the liver and kidney, and has been used in treating NAFLD however its molecular mechanisms remain elusive.

In a double-blind, randomized, parallel-group, placebo-controlled prospective clinical study, conducted by Miglio et al., evaluated efficacy and safety of oral betaine glucuronate in NAFLD were included 191 subjects, 96 subjects used betaine glucuronate combined with diethanolamine glucuronate and nicotinamide ascorbate, and 95 subjects used placebo during two months. The results demonstrated that the use of betaine glucuronate combined with diethanolamine glucuronate and nicotinamide ascorbate was effective in significant reduction of liver enzymes profile, hepatomegaly and NAFLD when compared to placebo. However, this study has limited value because histopathology was not used to diagnose NAFLD.

Abdelmalek et al. performed a pilot study to evaluate the safety and effects of betaine on hepatic biochemical profile and histological markers of NAFLD activity in 10 subjects with previously untreated, with biopsy-proven NAFLD. The study lasted 12 months, and 7 out of 10 patients completed 1 year of treatment with betaine. There was a significant improvement in liver enzymes profile, in the degree of steatosis, necroinflammatory grade, and...
sive and histological response.

Betaine seems to improve liver enzymes profile, homocysteine levels, and histological response. In this study of NASH patients, the betaine seems to improve liver enzymes profile, homocysteine levels, and histological response.

**N-Acetyl-cysteine (NAC)**

Regarding NASH disease treatment, antioxidant therapy by NAC has to be considered. NAC is a modulator of thiol levels, increasing intracellular glutathione especially in hepatic tissue, protecting against hepatotoxic agents. Thus, the NAC is a glutathione precursor which increases glutathione in hepatocytes and limits the reactive oxygen species that causes hepatocellular injury.

Study for evaluate the role of NAC in the process of liver injury, performed by Khoshbaten et al., includes 30 patients with NASH that were randomly selected to receive either NAC or vitamin C. Were evaluated liver enzymes profile and hepatobiliary system ultrasound, with follow-up for three months using the same methods of exams. At the end of the study was observed who NAC use resulted in a significant improve of liver enzymes profile compared to vitamin C, but no significant change was observed in the grade of steatosis of liver at ultrasound.

**Silymarin**

The active essence of silybun marianum plant known as silymarin and its use for diseases of the liver and biliary tract has been used for centuries. The silymarin presents 4 different mechanisms of action: antioxidants and regulators of intracellular content of glutathione; cell membrane stabilizers and permeability regulator; promoter of ribosomal RNA synthesis, stimulatory hepatic regeneration; and as inhibitor of stellate hepatocyte transformation into myofibroblasts.

Solhi et al., in a randomized clinical trial to evaluate the efficacy of silymarin in the treatment of NASH included 64 patients divided in 33 patients of case group who received 210 mg/day silymarin orally for 8 weeks and 31 patients in the control group who received placebo. Were included patients with NASH confirmed by sonography, and liver enzymes profile persistent elevation within the last six months. After 8 weeks, liver enzymes profile was measured and the patients of case group (silymarin) presented significant fall in liver enzymes profile.

Cacciapuoti et al. conducted a study to analyze the hepatic effects of silymarin on NASH in which they were included 72 subjects with NASH. Liver enzymes profile, hepatic echography and anti-inflammatory parameters were evaluated after 3 months of a restricted diet and before silymarin use 3.5 grams/day orally. After 6 months of treatment were repeated liver enzymes profile, hepatic echography and anti-inflammatory parameters, observing improve of liver enzymes and hepatic echography, on the contrary of anti-inflammatory parameters that not significantly reduced in the end of the study.

Aller et al. performed a randomized clinical pilot study for evaluate effects of silymarin plus Vitamin E in patients with NASH enrolled a sample of 36 subjects with liver biopsy-confirmed who were randomized in 2 groups: group I treated with 1080.6 mg of silymarin plus Vitamin E 72 mg per day besides lifestyle modification program and exercise for 3 months, and group II oriented only with a lifestyle modification program and exercise. In both groups, biochemical parameters, liver enzymes profile, and non-invasive NASH-index, as well as anthropometric parameters were evaluated before and after the treatment. The results showed that silymarin plus Vitamin E use and a hypocaloric diet improved function hepatic parameters, and non-invasive NASH index.

**Beta-carotene**

Beta-carotene, a lipid-soluble antioxidant, has an important function as a precursor of vitamin A, and it has a direct impact on cholesterol synthesis, moreover, serves as a pre-hormone that, through metabolism, becoming in retinoic acid, which functions as a ligand, regulating the expression of genes involved in metabolic processes. Considering the role of oxidative stress in NASH pathogenesis and the potent action of beta-carotene as a precursor of vitamin A in the fight against reactive oxygen species, it is probable that individuals with NASH will have lower levels of this vitamin. The beta-carotene is a potent antioxidant, and has been evaluated as a protective agent in NASH.

Erhardt et al. conducted a study with the objective of compare plasma levels of the antioxidants a-tocopherol, gamma-tocopherol, lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene and beta-carotene between 57 patients with biopsy-confirmed NASH and 40 healthy controls. The plasma levels of beta-carotene were significantly lower in NASH group than in group...
control. The results observed showed that the reduction of carotenoid levels induces to oxidative stress that a fundamental role in the pathogenesis of NAFLD, and therefore the supplementation of carotenoid antioxidants may be a treatment option for NAFLD.

In a study conducted by Park et al. to investigate the associations between NAFLD with metabolic syndrome and the serum carotenoids, were included 350 patients that were divided into 3 groups of according to fat accumulation hepatic degree, classified in normal, mild and severe by ultrasonography. There has been a statistically significant correlation among the metabolic syndrome and NAFLD, as well as level the serum beta-carotene reduction was associated with degree fat accumulation hepatic.

**ANTI-TUMOR NECROSIS FACTOR AGENTS**

Pentoxifylline

Pentoxifylline is a methylxanthine derivative and non-selective phosphodiesterase inhibitor that has been reported to have antioxidant activity and decrease tumor necrosis factor (TNF)-α gene transcription. Pentoxifylline has been used to treat NAFLD due to its anti-TNF-α effects, reduction of production of other pro-inflammatory cytokines, and shows anti-inflammatory properties, through the inhibition of nuclear factor-kappa B. It is non-selective phosphodiesterase inhibitor that has been reported to have antioxidant activity and decrease tumor necrosis factor (TNF)-α gene transcription.

Pentoxifylline use compared to placebo was associated with degree fat accumulation hepatic.

**PROBIOTICS**

A probiotic is a live microbial culture or cultured dairy product, which plays a fundamentally important role in health and disease. It has the premise that impairment of intestinal porosity through probiotics occurs to maintain or increase the absorption proteins at the intestinal mucosa cells. Findings from recent years show the relevance of the gut-liver-adipose tissue axis role in the pathogenesis of NAFLD.

The involvement of intestinal flora in pathogenesis of NAFLD has been widely studied, and manipulation of microbiota with therapeutic purpose is expanding very quickly. The association between increased intestine permeability and NAFLD in human was first described in 2009 by Miele et al. that demonstrated the relation of NAFLD with the increased prevalence of small bowel bacterial overgrowth in the evaluated patients.

An open-label, randomized controlled study, performed by Wong et al. for evaluate if treatment with probiotics it is more effective who usual care in reducing liver fat in NAFLD subjects, was performed in 20 patients with biopsy-proven NAFLD that were randomized to receive for 6 months a probiotics formula containing Lactobacillus plantarum, Lactobacillus deslridek, Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacterium bifidum. The intrahelatic triglyceride content measured by protonmagnetic resonance spectroscopy, liver enzymes and metabolic profile were evaluated at baseline and after treatment. The results showed statistically significant improvement of the evaluated parameters in NAFLD patients with the probiotics use.

Alisi et al. studied 44 obese children with histology-proven NAFLD by 4 months in a double-blind randomised controlled study for evaluate the effect of association of eight probiotic strains (VSL#3) vs. placebo on NAFLD. Anthropometrical data, fasting glucose and insulin, IR, total cholesterol and fractions, triglycerides, liver enzymes profile, total and activated Glucagon-like peptide-1 (GLP-1) and ultrasound data were performed at baseline and end 4 months from the initiation of study. The results showed that short term supplementation with VSL#3 significant improvement of NAFLD in children.

**CYTOPROTECTIVE AGENTS**

Ursodeoxycholic acid

Thus, the mechanisms antiinflammatory and anti-cholestatic effects of Ursodeoxycholic acid (UDCA) occurs because there is an activation the canalicular bile salt export pump, ATP-binding transporter B4 and baso-lateral multidrug resistance-associated protein. Also, the replacement of hydrophobic bile acids with hydrophilic UDCA appears to reduce the injury of the hepatic and biliary cells.
Studies have evaluated the therapeutic benefit of UDCA in patients with NAFLD, and in all studies, it was observed that liver tests, post-treatment liver biopsies, and degree of hepatic steatosis significantly improved when compared with baseline. 

Parkh et al.\textsuperscript{69} conducted a study comparing the efficacy of Vitamin E vs. UDCA randomizing 250 subjects non-cirrhotic and non-diabetic with NAFLD in two groups, a group with 100 subjects received Vitamin E 400 mg twice a day compared with another group with 150 subjects that received UDCA 300 mg twice a day for 52 weeks. The subjects had elevated liver enzymes and NAFLD diagnosed by ultrasound. The study evaluated the liver enzymes profile normalization, decrease of hepatic fibrosis score besides symptomatic improvement and tolerability. The study results showed that UDCA use can be an effective and safe alternative compared to Vitamin E in non-diabetic and non-cirrhotic subjects with NAFLD\textsuperscript{69}.

Another study performed by Pietu et al.\textsuperscript{70} with the objective of evaluate over a period of 10 years the tolerability and efficacy of UDCA with Vitamin E combination in patients with NAFLD, included 101 adult subjects with persistent elevation of hepatic enzymatic profile, and with biopsy-proven NAFLD. The results showed that the association of UDCA with Vitamin E presented a significant improve the liver enzymes profile to long-term and good tolerability\textsuperscript{70}.

Troisi et al.\textsuperscript{71} evaluated the efficacy of UDCA in 87 subjects in age range geriatric patients metabolic syndrome carriers and NAFLD or NASH for 6 months. The laboratory data and ultrasonography were used for diagnosis of steatosis. The patients were randomized into two groups, an UDCA-treated group and other diet-treated group. The parameters following were evaluated before and after treatment: ultrasonography hepatic, lipids and liver enzymes profile, symptoms and BMI. All patients with metabolic syndrome had liver steatosis, and after use of UDCA and diet the parameters evaluated improved significantly at 3 months. At the end of the study besides the improvement of NAFLD was no improvement of the metabolic syndrome parameters\textsuperscript{71}.

- **NOVEL TREATMENTS**

  **Renin-Angiotensin System blockers**

  The renin-angiotensin system plays an important role in hepatic fibrogenesis, and therapies with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) are now in widespread clinical use and have been shown to reduce tissue injury and fibrosis independently of their effects on blood pressure\textsuperscript{72}.

  There are indications that the renin-angiotensin-al-dosterone system favors the pathogenesis of NAFLD and indicates that ACE-I and ARBs can be a potentially useful therapeutic approach.\textsuperscript{73}

  A study to evaluate the effectiveness of losartan use in NAFLD includes 7 subjects with NAFLD and hypertension that were treated with 50 mg/d of losartan for 48 weeks was conducted by Yokohama et al.\textsuperscript{74} Before treatment, was demonstrated abnormally in liver enzymes profile, IR and liver histology in all patients. The results showed that losartan use improved significantly the blood markers of liver fibrosis, liver histology, as well as in liver enzymes profile. These results raise the possibility that losartan use in NAFLD and hypertensive may be efficacious for NAFLD treatment.\textsuperscript{74}

  Another study performed by Georgescu et al.\textsuperscript{75} evaluated the resulted of treatment with telmisartan vs. valsartan for 20 months in 54 patients with NAFLD and mild-to-moderate hypertension on the IR, cytolysis and NAFLD. The patients were randomized into 2 groups, a valsartan group with 26 patients that that used 80mg/day and a telmisartan group with 28 patients that used 20mg/day. Metabolic syndrome parameters by NCEP-ATP III criteria and liver-biopsy proven steatohepatitis were demonstrated in all patients. Liver enzyme and lipids profile, IR, BMI and blood pressure were analyzed at the beginning and every 4 months until the end of treatment. The results demonstrated that telmisartan use improved the cytolysis and IR, although it does not has normalized liver enzymes profile. This improvement was also associated with a significant decrease of NAFLD degree as well as improvement of lipid profile. In respect to valsatan group despite of improvement of liver enzymes profile and IR, there was no improvement in liver histology and had no effect on lipids profile. The results obtained in this study showed that the telmisartan presents a higher efficacy for IR and hepatic histology when compared with the valsartan.\textsuperscript{75}

  **Oligofructose**

  Oligofructose also known as oligofructan, short-chain fructan acquired from chicory root inulin, is a mix of nondigestible/fermentable fructooligosaccharides.\textsuperscript{76} Studies in experimental animals suggest that the addition of oligofructose in the diet improved in NAFLD, and has also been evaluated in humans.

  For investigate the effect of daily ingestion of oligofructose, Daubioul et al.\textsuperscript{77} studied 7 patients with NAFLD, confirmed by liver biopsies, who received 16 g/day of oligofructose or maltodextrine for 8 weeks in a randomized double-blind crossover design. Energy intake, body composition, liver steatosis and blood parameters were appraised after 4 and 8 weeks of dietary supplementation. This pilot study supports the putative interest of oligofructose in the management of liver diseases associated with abnormal lipid accumulation in humans\textsuperscript{77}.

  **Incretin Modulators**

  Two incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide, stimulate glucose-mediated insulin production in pancreatic beta cells. Clinical evidences show that GLP-1 analogues and inhibitors of dipeptidyl

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peptidase 4 can improve hepatic steatosis. Numerous hepatocyte signal transduction pathways appear to be activated by GLP-1 and its analogues, where the Akt and AMP-activated protein kinase seem to be the main factors in improving hepatic steatosis. GLP-1 appears to protect hepatocytes from fatty acid-related death by suppressing dysfunctional endoplasmic reticulum stress responses. Moreover, GLP-1 suppresses hepatic lipogenesis by activating the AMP kinase pathway and reduces hepatic fat accumulation and nutrient-induced hepatic proinflammatory responses.

Fukuhara et al.79 analyzed effectiveness and security of sitagliptin in NAFLD patients with type 2 diabetes mellitus (DM2) evaluating 44 patients with biopsy-proven NAFLD. To patients were administered sitagliptin 50 mg/day for 12 months. The study evaluated the hemoglobin A1c (HbA1c) and the liver enzymes profile. The results showed a positive correlation between improvement of HbA1c and improvement of liver enzymes. At the end of the study was observed that adequate glycemic control with sitagliptin contributes to the improvement of NAFLD79.

A study with the objective of evaluate efficiency of treatment with liraglutide on NAFLD in DM2 patients, comparison was made with sitagliptin and pioglitazone including 82 Japanese NAFLD patients with DM2 that were divided into 3 groups: liraglutide-treated group with 26 patients, sitagliptin-treated group with 36 patients, and pioglitazone-treated group with 20 patients, was performed by Ohki et al.80 All patients were treated for 5 months, comparing the laboratory results, as well as body weighs before and after treatment. At the end of fifth month of the follow-up, the liraglutide-treated group showed significant improvement of T2DM and also improves of NAFLD and decrease of body weight compared with the other 2 groups80.

Second generation sulfonylureas

NAFLD in general is associated with IR and obesity, and occurs commonly with DM2. Sulfonylureas such as nateglinide, has been considered a treatment option for NAFLD.

Study conducted by Morita et al.81 evaluated the nateglinide use in NAFLD patients and with DM2 who had failed to respond adequately to diet and exercise therapy, were compared the resulting changes in insulinemia and improvements in glycemia, as well as the concomitant variations in liver enzymes profile, diagnostic liver images and liver biopsy, with the results from a non-treated control group. The sample included 10 patients with NAFLD all with DM2. The patients were diagnosed with NAFLD by abdominal ultrasonography, computed tomography and liver biopsy. The patients were compared into two groups, a nateglinide-treated group and a control group. Each group contained five patients. The members of the nateglinide-treated group were administered nateglinide 270mg/day before each meal for a period of 20 weeks.

The two groups continued to receive diet and exercise therapy. BMI, blood chemistry, plasma glucose and HbA1c, abdominal ultrasonography and computed tomography were measured before treatment, and every four weeks thereafter. Liver biopsy was performed once again at the end of the treatment. From of the results concludes that nateglinide is useful in the treatment of NAFLD in patients with DM281.

A evaluation showed that of the 150 million off-label prescriptions in the United States, 73% had little or no scientific support82.

CONCLUSION

After analyzing the data, may conclude that literature includes studies that provides scientific evidence for the off-label use in NAFLD. However, randomized, placebo controlled studies should be performed to confirm this evidence.

Actually, does not have on-label treatment for NAFLD. This study presented scientific evidence for off-label use of medications in NAFLD, based in several therapeutic studies encouraging with clinically relevant end-points. The evidence of the evaluated studies, suggest that metformin treatment has best effect on reducing hepatocyte fat deposition with regard to other drugs evaluated.

Off-label prescriptions of medication are common from day to day, and most occurs without scientific support. However, off-label prescribing remains acceptable if there is no suitable alternative and physicians are secure that they are using agents in accordance with a respected medical opinion.

The studies required to determine the off-label use in NAFLD is justified by good scientific evidence described in this manuscript. Nevertheless, the physician should be aware of the uses and limitations of treatment, and the patient should be made aware as well.

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