

Off-label treatment in diabetic retinopathy

Tratamento Off-label na retinopatia diabética

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Abstract

Introduction: The prescribing a drug without the indications for which the drug was originally approved by regulators is internationally known as prescribing “off-label”. **Objective:** To describe the off-label therapy in diabetic retinopathy, reported international scientific literature, through an integrative bibliographical review. **Method:** Integrative review by searching the Medline international database for review of manuscripts. **Results:** A total 852 scientific productions were identified, and 37 studies were selected by contain information about the off-label therapy in diabetic retinopathy. **Conclusion:** The practice of off-label prescribing in diabetic retinopathy has benefits, and in some situations is the only treatment available.

Keywords: Diabetic retinopathy. Off-label use. Therapy. Diabetes mellitus.

Resumo

Introdução: A prescrição de um medicamento sem indicações para os quais a droga foi originalmente aprovada pelos órgãos reguladores é conhecida internacionalmente como uma prescrição “off-label”. **Objetivo:** Descrever o tratamento off-label da retinopatia diabética, relatados literatura científica internacional, através de uma revisão bibliográfica integrativa. **Método:** Revisão integrativa através de pesquisa na base de dados internacional Medline para revisão de manuscritos. **Resultados:** Um total de 852 produções científicas foram identificados e 37 estudos foram selecionados por conter informações sobre o tratamento off-label na retinopatia diabética. **Conclusão:** A prática de prescrição off-label na retinopatia diabética tem benefícios e em algumas situações é o único tratamento disponível.

Palavras-chave: Retinopatia diabética. Uso off-label. Terapia. Diabetes mellitus.

INTRODUCTION

Many drugs are prescribed outside the terms of the marketing authorization (“off-label”) from that approved by the health agency. Off-label use of drugs is relatively common in medical practice, even if it’s often not supported by strong scientific evidence. Off-label therapy is defined as the use of medications for indications that is not mentioned in the approved labeling of the drug; using a drug outside of the recommended dosage range or duration of use; using a drug in certain unapproved patient populations, such as those defined by age, sex, or particular clinical parameters, or intentionally using a medication in a patient who has a known contraindication. It is legal,

but there are implications for prescribers, outlined by regulatory bodies of health. Several studies have shown that this is a common practice in various healthcare settings, and studies in the United States have shown that off-label use may account for approximately 20% of prescriptions, or 150 million prescriptions per year^{1,2}.

Three broad categories of appropriate off-label use are identified: off-label use justified by high-quality evidence; use within the context of a formal research proposal; and exceptional use, justified by individual clinical circumstances³.

The off-label medications use occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (for example, pediatric, pregnant, or psychiatric patients)⁴.

In this article we report the studies available in literature of current administration off-label medications in diabetic retinopathy, through an integrative bibliographical review.

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METHODS

Sample delimitation

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

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 the scientific production devoted to the topic over the timeframe under analysis. The following inclusion criteria were considered during the review: articles published between January 1980 and November 2013; use of the keywords "off-label use" OR "off-label " OR "off-label prescribing" MeSH "diabetic retinopathy" entered into the search form; and availability of an abstract in English. Articles were assessed and classified according to predetermined categories, especially types of markers analyzed. With these documents in hands, an analytical reading was done and the papers organized by drugs.

RESULTS

A total 852 scientific productions were identified, and 37 studies were selected by contain information about the off-label therapy in diabetic retinopathy.

We describe below the off-label drugs used for diabetic retinopathy.

DISCUSSION

Diabetic retinopathy is composed of a characteristic group of lesions found in the retina of individuals having diabetes mellitus for several years, being defined as a neurovascular rather than a micro-vascular disease as neurodegenerative disease precedes and coexists with micro-vascular changes. Apart from its effects on vision, the presence of diabetic retinopathy also signifies a heightened risk of life-threatening systemic vascular complications⁵.

The recent advances in understanding the complex pathophysiology of diabetic retinopathy allowed the physician to identify many cell types involved in its pathogenesis being that the vasoactive and pro-inflammatory molecules, such as vascular endothelial growth factor play a key role. Furthermore, other agents directing to the processes of vasopermeability and angiogenesis, are under investigations, giving more hope in the future management of this still sight-threatening disease⁶.

The classification proposed during an International Congress of Ophthalmology in Sydney in April 2002, includes the following stages: no apparent diabetic retinopathy; mild non-proliferative diabetic retinopathy; moderate non-proliferative diabetic retinopathy; severe

non-proliferative diabetic retinopathy; and proliferative diabetic retinopathy⁷.

Strict metabolic control, tight blood pressure control, laser photocoagulation, and vitrectomy remain the standard care for diabetic retinopathy⁸. Good glycaemic control can attenuate the development of diabetic retinopathy but such metabolic control is often difficult to achieve and maintain and additional therapies need to be identified by which retinopathy can be prevented or arrested. The discovery recent of inhibitors of vascular endothelial growth factors is revolutionizing the management of diabetic retinopathy, particularly diabetic macular edema. However, not all patients respond to anti-vascular endothelial growth factors agents, reinforcing the fact that diabetic retinopathy is a multifactorial disease⁵. Off-label therapies include anti-oxidants agents, antiplatelet agents, bevacizumab, corticosteroids, fenofibrate, lisinopril, pegaptanib, pentoxifylline, ranibizumab, and statins.

Anti-oxidants agents

Oxidative stress is increased in the retina in diabetes. The possible sources of increased oxidative stress might include increased generation of free radicals or impaired anti-oxidant defense system. Antioxidants are also known as free radical scavengers. In our body free radical production is balanced by the anti-oxidative defense system and imbalance between reactive oxygen species generation and its neutralization by anti-oxidant defenses creates oxidative stress⁹. Thus, the retina operates in a highly oxidative environment and requires an efficient anti-oxidant system to prevent mitochondrial and cellular stresses. Anti-oxidants can inhibit the oxidative processes and protect retinal cells from ischemic/hypoxic insults. Treatment using anti-oxidants such as vitamin E are possible therapeutic regimens for diabetic retinopathy¹⁰. A study showed that oral antioxidant supplementation may be a useful adjunct long-term therapy for patients with type 2 diabetes who have non-proliferative diabetic retinopathy¹¹. Although anti-oxidants appear to be promising in inhibiting the development of diabetic retinopathy in animal models, but further clinical studies are needed to determine the appropriate regimen, and also whether these therapies could have long-term effects that may slow the progression of this sight-threatening complication of diabetes. Although anti-oxidants agents appear to be promising in inhibiting the development of diabetic retinopathy in animal models, but further clinical studies are needed to determine the appropriate regimen, and also whether these therapies could have long-term effects that may slow the progression of this sight-threatening complication of diabetes. Nevertheless, despite of absence of current scientific clinical trials for use of anti-oxidants agents in diabetic retinopathy, based on pharmacological effects described above the medical practitioners are free to prescribe anti-oxidants agents for off-label uses in diabetic retinopathy.

Antiplatelet agents

Aspirin is a potent anti-inflammatory agent that acts not only by inhibiting the enzymatic activity of cyclooxygenases by acetylation, but also by inhibiting the activation of some transcription factors¹². It has been reported that aspirin inhibits the development of diabetic retinopathy in diabetic animals, raising the possibility that anti-inflammatory drugs may have beneficial effects on diabetic retinopathy¹³. Aspirin therapy to a diabetic patient is helpful in preventing diabetic retinopathy. An experimental study about the effect of aspirin on diabetic retinopathy reveals that aspirin therapy may be used as a primary and secondary preventive measure for diabetic retinopathy. However, The Early Treatment Diabetic Retinopathy Study showed that 650 mg aspirin per day had no effect on the progression of retinopathy or the development and duration of vitreous hemorrhage. It was concluded that aspirin is not beneficial for the treatment of retinopathy, but there is normally no contraindication to its use in patients with retinopathy, when required for cardiovascular disease or other indications¹⁴. Thus, antiplatelet agents are currently off-label prescribed in the diabetic retinopathy with acknowledged benefits, resulting in slow of diabetic retinopathy progression with safety and efficacy.

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that binds to all isoforms and neutralizes the biologic activity of human vascular endothelial growth factor. Consequently, it prevents the interaction between vascular endothelial growth factor and its receptors on the surface of endothelial cells which starts the intracellular signaling pathway leading to endothelial cell proliferation and new blood vessel formation. The antibody was initially designed and studied as an anti-angiogenic strategy to treat a variety of solid tumors. The humanization decreases the risk for an immunological response and increases its half-life¹⁵. Intravitreal bevacizumab is used off-label for diabetic retinopathy¹⁶. Although intravitreal use of bevacizumab is off-label option, its use has risen exponentially in last few years, mainly due to its efficacy and economic consideration. Studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of vascular permeability and fibrovascular proliferation in macular edema secondary to central vein occlusion, retinal neovascularization secondary to proliferative diabetic retinopathy, and choroidal neovascularization secondary to age-related macular degeneration¹⁷. Study recent to evaluate the anatomical and functional outcomes at 24 months in patients with diffuse diabetic macular edema treated with primary intravitreal bevacizumab plus grid laser photocoagulation or primary intravitreal bevacizumab alone or grid laser photocoagulation alone, provides evidence to support the use of primary intravitreal bevacizumab with or without grid

laser photocoagulation as treatment of diffuse diabetic macular edema¹⁸. Therefore, in the treatment of diabetic retinopathy the use of intravitreal bevacizumab, yet that off-label has special advantages.

Corticosteroids

Corticosteroids are a class of chemicals of hormones produced in the adrenal cortex and analogues of these hormones that are synthesized in laboratories. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Intraocular steroids have been in use since the 1970s, when adjunctive use of dexamethasone was reported to decrease inflammation in eyes with postoperative or post-traumatic bacterial endophthalmitis¹⁹. Off-label intravitreal corticosteroids are associated with short-term anatomic and visual improvement in some patients, but these patients may require repeated intravitreal injections with cumulative risks of cataract formation, intraocular pressure elevation, and endophthalmitis²⁰. The studies showed that until 42% of patients get visual acuity improvement with the use of intravitreal corticosteroids, and in 5-year follow-up, patients who responded to intravitreal corticosteroids maintained their visual acuity gains²¹. Triamcinolone is a synthetic glucocorticoid, with low solubility in aqueous solution, with rapid bioavailability and sustained-release characteristics, and that can inhibit not only inflammation and proliferative response in proliferative retinopathy but also the inflammation required for healing. The use of intravitreal triamcinolone to treat diabetic retinopathy has emerged as an increasingly common treatment for certain patients, being introduced into clinical use in 1979 as a treatment for refractory diabetic macular edema due to its effect of attenuating the vascular endothelial growth factor mediated retinal capillary permeability that is presumed to be a contributing factor in its pathogenesis, and has proven to be effective in improving vision, reducing macular thickness and inducing reabsorption of hard exudates^{22,23}.

Dexamethasone is a potent, water-soluble corticosteroid that can be implanted to the vitreous cavity by the dexamethasone intravitreal implant. This implant is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone that gradually releases the total dose of dexamethasone over a series of months after insertion into the eye through a small pars plana puncture using a customized applicator system²⁴. Dexamethasone intravitreal implant was approved by the FDA may be indicated medically for the treatment of: non-infectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, macular edema following branch or central retinal vein occlusion. All other uses of a corticosteroid intravitreal implant are considered off-label, including

the treatment of diabetic macular edema. Finally, studies showed that the treatment with dexamethasone intravitreal implant exhibit clinically and statistically significant improvements in both vision and vascular leakage from diabetic macular edema in vitrectomized eyes and has an acceptable safety profile.

Fluocinolone is a synthetic hydrocortisone derivative. The fluorine substitution at position 9 in the steroid nucleus greatly enhances its activity. In ophthalmology, the fluocinolone reduce retinal inflammation and may restore the integrity of the blood–retina barrier by increasing tight-junction protein expression²⁵. Hence, fluocinolone acetonide intravitreal implant is off-label indicated for the treatment of vision impairment associated with chronic diabetic macular edema considered insufficiently responsive to available therapies. The FAME (Fluocinolone Acetonide in Diabetic Macular Edema) study was a prospective-randomized, double-masked, multicenter trials assessing sustained-release fluocinolone acetonide, where all study participants had persistent diabetic macular edema despite at least one macular laser treatment. At follow-up, mean best corrected visual acuity improvements for the low- and high-dose groups compared with the sham group. The cataract and glaucoma surgery were more prevalent for the implant groups²⁶.

So the results of the studies support that the off-label treatment with intraocular steroids in diabetic patients, may prevent or delay the progression of diabetic retinopathy.

Fenofibrate

Fenofibrate is a drug of the fibrate class and its chemical name of propan-2-yl 2-[4-[(4-chlorophenyl) carbonyl]phenoxy]-2-methylpropanoate. It is a peroxisome proliferator–activated receptor (PPAR)-agonist indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia, and also has shown robust protective effects against diabetic retinopathy in DM2 patients²⁷. Moreover, it has been demonstrated that fenofibrate prevents the apoptosis of human retinal endothelial cells induced by serum deprivation through a PPAR-independent but AMP activated protein kinase-dependent pathway²⁸. Two trials indicated that fenofibrate has an anti-inflammatory and anti-atherosclerotic effect on the artery wall in addition to a lipid-modifying effect that may slow the progression of diabetic retinopathy, but the exact mechanisms underlying the beneficial effect on diabetic retinopathy remains uncertain²⁹. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included a lipid management arm, and the ACCORD-EYE sub-study, randomization to fenofibrate was associated with a significant reduction in the risk of progression of diabetic retinopathy, that confirm and extend the results together with those of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, in which DM2 patients randomized to fenofibrate benefited from a significantly lower incidence of laser treatment for

retinopathy, progression of retinopathy or a composite measure of retinopathy outcomes^{30,31}.

Although fenofibrate is indicated for hypertriglyceridemia treatment, off-label use for diabetic retinopathy is under investigation, because the clinical practice has shown that fenofibrate reduces the progressive dysfunction vascular in diabetic retinopathy.

Pegaptanib

Pegaptanib sodium is an anti-vascular endothelial growth factor ribonucleic acid aptamer, being the first aptamer to be successfully developed as a therapeutic agent in humans. It specifically binds to vascular endothelial growth factor isoform 165, a protein that plays a critical role in angiogenesis and increased permeability. It was FDA approved in December 2004, for the treatment of all types of neovascular age-related macular degeneration, and has been off-label used in treatment of diabetic retinopathy³². The ability of intravitreal pegaptanib to induce regression of retinal neo-vessels in diabetic retinopathy was first demonstrated in 2009, when it was used injections of 0.3 mg pegaptanib every 6 weeks for 30 weeks, showed that intravitreal pegaptanib was able to induce regression of retinal neovessels within three weeks in 90% of treated patients³³.

Our study found only one trial demonstrated that pegaptanib was effective in diabetic retinopathy when applied intravitreal.

Pentoxifylline

Pentoxifylline is a methylxanthine phosphodiesterase inhibitor with anti-inflammatory effects and immune-regulatory properties³⁴. Pentoxifylline has how mechanism of action decrease blood viscosity by increasing red blood cell flexibility and reducing serum fibrinogen levels. Thus, this drug correct impaired erythrocyte deformability and mainly affect blood flow in small vessels and capillaries, taking haemorrhological changes and influencing in outcome and progression of diabetic retinopathy. Some studies have shown a lower incidence of retinal neovascularization in diabetic patients treated with pentoxifylline³⁵. Some studies have shown a lower incidence of retinal neovascularization in diabetic patients treated with pentoxifylline. Other studies showed the potential efficacy of pentoxifylline in improving ocular blood flow in patients with diabetic retinopathy, demonstrating that pentoxifylline increases retinal capillary blood flow velocity in patients with diabetes³⁶.

Therefore, pentoxifylline are currently off-label prescribed in the diabetic retinopathy with acknowledged benefits resulting from the fact that can improve ocular blood flow with safety and efficacy.

Renin-angiotensin system blockers

The renin-angiotensin system is activated by chronic hyperglycemia, and the vitreous fluid level of angiotensin II is elevated in patients with proliferative diabetic

retinopathy and diabetic macular edema. It has been suggested that an autocrine-paracrine relationship may exist between angiotensin II and vascular endothelial growth factor in the ocular tissues. Accordingly, angiotensin-converting enzyme inhibitors or AT1 receptor blockers may be useful therapeutic agents for preventing the progression of diabetic retinopathy³⁷. The findings of the Eurodiab Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID) suggested that blockade of the renin-angiotensin system with the angiotensin-converting enzyme inhibitor lisinopril could reduce both incidence and progression of retinopathy in type 1 diabetes³⁸. Likewise, the Diabetic Retinopathy Candesartan Trials (DIRECT) demonstrated that the angiotensin-receptor antagonist candesartan reduced the incidence of retinopathy in patients with type 1 diabetes³⁹, and might induce improvement of retinopathy in type 2 diabetic patients with mild-to-moderate retinopathy⁴⁰.

The angiotensin converting enzyme inhibitors decrease the rate of progression of diabetic retinopathy in patients with diabetes, and these beneficial effects are independent of the antihypertensive properties of these drugs. The results of studies support that off-label treatment with renin-angiotensin system blockers in diabetic patients, may prevent or delay the progression of diabetic retinopathy.

Statins

Statin is 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis, and are frequently used lipid-lowering drugs in DM2, because besides hyperglycemia and hypertension, a recently recognized risk factor for diabetic retinopathy appears to be hyperlipidemia. Few studies have evaluated statins in diabetic retinopathy it is still unclear whether the beneficial effects of statins in diabetic retinopathy are related to their lipid-lowering properties or their pleiotropic effects on vascular endothelial growth factor-induced signaling pathway⁴¹. The beneficial effect of statins on retinopathy in diabetic patients was reported for the first time in 1991 in six patients, where pravastatin improved the appearance of hard exudates and micro-aneurysms⁴². In later studies, simvastatin improved visual acuity in diabetic patients with hypercholesterolemia, and atorvastatin prevented the appearance of hard exudates and micro-aneurysms in patients with diabetic macular edema, beyond improve retinal blood flow velocities in patients with background or proliferative diabetic retinopathy⁴³. Therefore, according to these data the statins may be potential options for the treat of diabetic retinopathy.

Ranibizumab

Ranibizumab is a monoclonal antibody fragment derived from the same parent mouse antibody as bevacizumab previously described. It is much smaller than the

parent molecule and has been affinity matured to provide stronger binding to VEGF-A. It is an anti-angiogenic that has been approved to treat the "wet" type of age-related macular degeneration a common form of age-related vision loss.

Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema, known as the Laser-Ranibizumab-Triamcinolone for Diabetic Macular Edema Study 2-year results demonstrated that ranibizumab with prompt or deferred focal/grid laser achieved superior visual acuity and optical coherence tomography outcomes compared with focal/grid laser treatment alone. In the ranibizumab groups, approximately 50% of eyes had substantial improvement and 30% gained 15 or more letters. Intravitreal triamcinolone combined with focal/grid laser did not result in superior visual acuity outcomes compared with laser alone, but did appear to have a visual acuity benefit similar to ranibizumab in pseudophakic eyes⁴⁴.

Recent study to evaluate intravitreal ranibizumab compared with intravitreal saline injections on vitrectomy rates for vitreous hemorrhage from proliferative diabetic retinopathy, concluded that overall, the 16-week vitrectomy rates were lower than expected in both groups. This study suggests little likelihood of a clinically important difference between ranibizumab and saline on the rate of vitrectomy by 16 weeks in eyes with vitreous hemorrhage from proliferative diabetic retinopathy. Short-term secondary outcomes including visual acuity improvement, increased panretinal photocoagulation completion rates, and reduced recurrent vitreous hemorrhage rates suggest biologic activity of ranibizumab. Long-term benefits remain unknown. Whether vitrectomy rates after saline or ranibizumab injection are different than observation alone cannot be determined from this study⁴⁵.

Ranibizumab, as well as, other intravitreal anti-vascular endothelial growth factor agents have emerged as off-label treatments in diabetic patients, may prevent or delay the progression of diabetic retinopathy.

CONCLUDING REMARKS

This study presented an integrative review on off-label drugs use in prevention, treatment, and complications of diabetic retinopathy (Table 1).

When a doctor prescribes a drug for a use, or in a manner, not authorized by the FDA is called off-label prescribing. Off-label treatment can be experimental, standard, or even state-of-the-art. It has become a part of main stream medical practice, with many off-label uses recommended by medical textbooks, research institutes, professional organizations, and standard pharmaceutical reference works. In the meantime, off label prescribing remains acceptable if there is no suitable alternative and physicians are confident that they are using agents in accordance with the body of respected medical opinion, and off-label prescribing has been common in most medical specialties.

The current system allows drugs that are safe and effective for one indication could be used for any other indications without adequate safeguards. However, prescription of drugs off-label does not should convert into experimental or investigational products, but a number of occasions such off-label treatments have proven to be

essential to the successful treatment of some very serious illnesses. It is therefore at least conceivable that if such off-label uses are permitted, the drug may in reality be worthless or even dangerous for its alternative use, yet doctors may be freely employing it for that purpose.

Table 1 – Off-label drugs use in diabetic retinopathy

DRUG	CLINICAL EFFECT	REFERENCES
Anti-oxidants agents	Protects blood vessels and capillaries from free-radical damage.	Li, S.Y. ¹⁰ ; Garcia-Medina, J.J. ¹¹ .
Antiplatelet agents	Slow down progression of diabetic retinopathy with safety and efficacy	Zheng, L. ¹³ ; ETDRS ¹⁴ .
Bevacizumab Pegaptanib Ranibizumab	Improve vision in diabetic macular edema	Valiatti, F.B. ¹⁷ ; Arevalo, J.F. ¹⁸ ; Cunningham, E.T.Jr. ³³ ; Elman, M.J. ⁴⁴ ; Diabetic Retinopathy Clinical Research Network ⁴⁵ .
Corticosteroids	Slow down progression of diabetic retinopathy, improve vision in diabetic macular edema	Diabetic Retinopathy Clinical Research Network ²¹ ; Romero-Aroca P. ²² ; Machemer, R. ²³ ; Kuppermann, B.D. ²⁴ ; Campochiaro, P.A. ²⁶
Fenofibrate	Prevents the apoptosis of retinal endothelial cells	Touyz, R.M. ²⁹ ; Wright, A.D. ³⁰ ; Keech, A.C. ³¹
Renin-angiotensin system blockers	Attenuate the progression of diabetic retinopathy in non hypertensive type 1 diabetes	Funatsu, H. ³⁸ ; Chaturvedi, N. ³⁹
Pentoxifylline	Improve ocular blood flow with safety and efficacy	Baykara, M. ³⁶
Statins	Improved the appearance of hard exudates and micro-aneurysms	Samii, A. ⁴² ; Ozkiris, A. ⁴³

Thus, off-label drug use is just one aspect of the larger question about how to balance benefits, harms, and costs of medical interventions when technological advances are rapid, evidence is imperfect, and resources are finite.

Therefore, the use of off-label drugs in diabetic retinopathy is an alternative in the treatment of complications of diabetes, and its use has been demonstrated an improvement in signs and symptoms while specific medications yet not have been released for use on-label.

Competing interests: None declared.

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Submetido em 30.11.2013;

Aceito em 21.04.2014.