State of art of oral vitamin B12 (cobalamin) treatment in Biermer's disease (pernicious anemia)

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Abstract

In the setting of vitamin B12 (cobalamin) deficiency, new routes (oral and nasal) of vitamin B12 replacement have being developed and studied. In Biermer's disease, two prospective controlled randomized studies, a recent systematic review by the *Cochrane* group and four prospective studies were found and provide evidence that oral vitamin B12 treatment may adequately treat cobalamin deficiency. The efficacy was documented with a marked improvement in serum vitamin B12 levels or normalization of this latter. The clinical efficacy was also established with an improvement or a normalization of hematological parameters. The safety was documented in the majority of the studies. In this setting, oral replacement will be of interest for clinicians to avoid painful and administration difficulties, and cost of monthly injections. To date, effect of oral vitamin B12 treatment has not yet been adequately documented in patients presenting with severe neurological manifestations.

Introduction

Vitamin B12 (cobalamin) is the largest and most complex of all the vitamins [1]. Their molecular structure is $C_{63}H_{88}CoN_{14}O_{14}P$ or $C_{62}H_{88}CoN_{13}O_{14}P$ and their molecular weight is 1329.37 g/mol (Figure 1). The name vitamin B12 is generic for a specific group of cobalt-containing corrinoids with several essential biological activities in humans. Interestingly it is the only known metabolite to contain cobalt, which gives this water-soluble vitamin its red color. This group of corrinoids is also known as cobalamins.

The main cobalamins in humans and animals are hydroxo-, adenosyl- and methyl- cobalamin, the last two being the active coenzyme forms [2]. In fact, these compounds are necessary for hematopoiesis, neural metabolism, DNA and RNA production, and carbohydrate, fat, and protein metabolism.

To date, management of vitamin B12 deficiency with vitamin B12 injections is currently well established, but new routes of vitamin B12 administration, particularly oral and nasal, are being studied [3,4]. The treatment is based on cyano- and hydroxo-cobalamin in the form of tablets, injectable or oral solutions.

This narrative review summarizes the current knowledge on the efficacy and safety of oral vitamin B12 (cobalamin) treatment (replacement) in Biermer's disease (pernicious anemia).

References search

A literature search was performed on the *PubMed* database of the US National Library of Medicine and on *Scholar Google*. We searched for articles published between January 2010 and June 2018, using the following key words or associations: "vitamin B12", "cobalamin", "vitamin B12 deficiency", "cobalamin deficiency", "oral vitamin B12", "oral cobalamin", "oral vitamin B12 therapy", "oral cobalamin therapy", "Biermer's disease", "pernicious anemia"; restrictions included: English- or French-language publications; published from January 1, 2010, to July 1, 2018; human subjects; clinical trials, review articles or guidelines.

Additional studies were obtained from references of identified studies, the *Cochrane Library* and the *ISI Web of Knowledge*. Data gleaned from international meetings were also used, as information gleaned from commercial sites on the web.

All of the English and French abstracts were reviewed by at least 2 senior researchers from our research team (*CAREnce en vitamine B12* [*CARE B12*], in the University Hospital of Strasbourg, Strasbourg, France). After rigorous selection, only 37 papers were selected and analyzed. The latter were used to write this paper in the form of a narrative review.

Cobalamin metabolism and its abnormalities or defects

Cobalamin metabolism is complex and is made up of many processes, abnormalities or defects in any one of which can lead to vitamin B12 deficiency [1]. The different stages of cobalamin metabolism and corresponding causes of cobalamin deficiency are shown in Figure 1 [4,5]. In this setting, the best-known pathology is Biermer's disease also classically know as pernicious anemia.

Biermer's disease is an autoimmune gastritis resulting from the destruction of gastric parietal cells and consequent impairment of
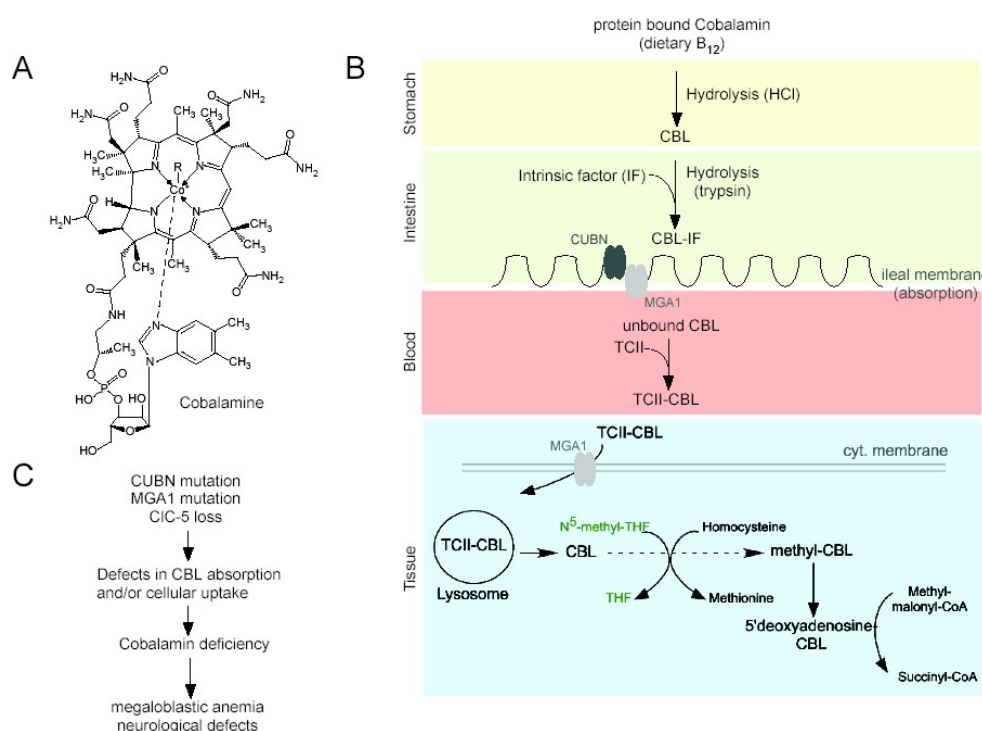
Figure 1. Structure (A) and metabolism of the vitamin B12 (B). The metabolic journey of cobalamin (cbl) from nutrient intake to its intestinal absorption. Endocytic receptors and proteins responsible for vitamin B12 intestinal absorption include cubilin (CUBN), amnionless (AMN), receptor-associated protein and megalin (MGA1). The membrane megalin/transcobalamin II (TCII)-receptor complex allows the cellular uptake of cbl. Lysosomal-mediated degradation of TCII and subsequent release of free-cbl is essential for vitamin B12 metabolic functions. MS, methonine synthase; THF, tetrahydrofolate; MTHFR, methylene tetrahydrofolate reductase; MCM, methylmalonyl CoA mutase [1,5]

intrinsic factors secretion to bind the ingested vitamin B12 [4,5]. In this setting, other autoimmune disorders are commonly associated as: thyroid disease (mainly Hashimoto's disease), Sjögren's syndrome, type 1 diabetes mellitus, vitiligo, even coeliac disease.

A typical Western diet contributes 3–30 μg of vitamin B12 per day towards the recommended dietary allowance of 2.4 μg par day for adults [5]. The 5–10-year delay between the onset of vitamin B12 deficiency and the development of clinical symptoms is directly attributable to hepatic stores of cobalamin (>1.5 mg) and the enterohepatic cycle [4,5].

In the context of this paper, it is important to know that between 1–5% of "free" cobalamin or "crystalline" cobalamin is absorbed by passive diffusion along the entire gastro-intestinal tract, from the oral or nasal mucosa to the colic mucosa [4,5]. Passive diffusion accounts for about 1% of total absorption, and this route of absorption is unaffected in patients with pernicious anemia. This absorption explains the mechanism underlying oral and nasal treatment of vitamin B12 deficiencies.

In humans, cobalamin participates in 2 enzymatic processes (Figure 1) [6]. First in the methionine synthase reaction, homocysteine is converted to methionine allowing for the "recycling" of 5-methyl-tetrahydrofolate (THF) to N5,10 methylene-THF which is needed for the *de novo* synthesis of thymidylic acid and ultimately, for DNA formation. Thus, homocysteine accumulates, methionine and in term S-adenosylmethionine decrease. This later limits N5,10-methylene-THF formation by decreasing the synthesis of formyl-THF. These modifications may limit many methylation reactions, including reactions involving DNA and myelin basic protein. Second in the methylmalonyl CoA mutase reaction, methylmalonyl CoA, derived from propionic acid synthesized by intestinal bacteria, is converted to succinyl CoA, a precursor for fatty acid and heme synthesis. Thus, cobalamin deficiency results in methylmalonic acid (MMA) accumulation.

These reactions explain the main clinical manifestation of vitamin B12 deficiency: megaloblastic anemia and neuro-cognitive abnormalities [1,2]. They also explain the elements of the definition of vitamin B12 deficiency. Thus, vitamin B12 deficiency is characterized by serum vitamin B12 levels <150 pmol/L (200 pg/mL) ± serum total homocysteine levels >13 μmol/L or urinary MMA >0.4 μmol/L [7].

Manifestations and etiologies of vitamin B12 deficiency in adults

Vitamin B12 deficiency is relatively frequent in elderly patients, around 2 to more than 30% according to depending on the target population, the design and location of the studies, but is often unrecognized or not investigated because the clinical manifestations of vitamin B12 deficiency are subtle [5]. Absolute vitamin B12 deficiency (established in regard of the aforementioned definition of vitamin B12 deficiency, mainly associated with documented clinical manifestation) occurs of at least 6% of adults (at least 60 years-old) and elderly patients. In these populations, a marginal deficiency occurs in around 20% of elderly subjects. In practice for clinicians, it is important to note that certain complications of vitamin B12 deficiency, in particular psycho-neurological and hematological complications are potentially serious, as seen in Table 1, and therefore require investigation in all patients who present with vitamin or nutritional deficiency.

In industrialized countries, disorders such as nutritional deficiencies, malabsorption or genetic cobalamin disorders are rare or exceptional etiologies of vitamin B12 deficiency, especially in adults [5]. In European countries, it has been estimated that the prevalence of Biermer's disease is approximately 4% of the population. Even outside the classic Biermer's disease, a more common problem is food-cobalamin malabsorption (FCM), a disorder characterized by the inability to release cobalamin from food or its binding proteins [8,9]. In

Table 1. Main clinical features of vitamin B12 (cobalamin) deficiency [1,2,5]

Hematological manifestations	Neuro-psychiatric manifestations	Digestive manifestations	Other manifestations
Frequent: macrocytosis, neutrophil hypersegmentation, aregenerative macrocytary anemia, medullar megaloblastosis ("blue spinal cord") *Rare*: isolated thrombocytopenia and neutropenia, pancytopenia *Very rare*: hemolytic anemia, thrombotic microangiopathy (presence of schistocytes)	*Frequent*: polyneuritis (especially sensitive), ataxia, Babinski's phenomenon *Classic*: combined sclerosis of the spinal cord *Rare*: cerebellar syndromes affecting the cranial nerves including optic neuritis, optic atrophy, urinary and/or fecal incontinence *Under study*: changes in the higher functions, dementia, stroke and atherosclerosis (hyperhomocysteinemia), parkinsonian syndromes, depression, multiple sclerosis	*Classic*: Hunter's glossitis, jaundice, LDH and bilirubin elevation ("intramedullary destruction") *Debatable*: abdominal pain, dyspepsia, nausea, vomiting, diarrhea, disturbances in intestinal functioning *Rare*: resistant and recurring mucocutaneous ulcers	*Frequent*: tiredness, loss of appetite *Under study*: atrophy of the vaginal mucosa and chronic vaginal and urinary infections (especially mycosis), hypofertility and repeated miscarriages, venous thromboembolic disease, angina (hyperhomocysteinemia)

several recent studies, FCM and Biermer's disease are the main causes of vitamin B12 deficiency in adults and elderlies (between 70 to 80%) [9].

In this relatively recent description syndrome of FCM, at least in its complete form, the absorption of unbound ("free" or crystalline) cobalamin remains normal (Figure 1) [8]. This maldigestion produces a more slowly progressive and long-term partial depletion of vitamin B12 stores. In comparison, Biermer's disease leads to a more rapid and complete depletion of the cobalamin store, engendered by disruption of intrinsic-factor-mediated absorption [8,9]. This may explain the subtle manifestations of the FCM in some patient, especially in the early stages.

The partial nature of this form of malabsorption (bound-cobalamin) explains that oral vitamin B12 may be effective to cure the deficiency. This also explains why the required treatment dose of oral vitamin B12 may be lower in FCM than in Biermer's disease [10].

Parenteral vitamin B12 treatment

The classic treatment for vitamin B12 deficiency is by parenteral administration, as intramuscular (IM) injections in main countries, in the form of cyano- and, more rarely, hydroxyl- (also called hydroxo-) or methyl-cobalamin, especially for this later for the treatment of genetic deficiencies [10,11].

This mode of administration is explained by the fact that the 2 main etiologies of vitamin B12 deficiencies were historically the pernicious anemia and the malabsorption, in particular following gastrectomy for stomach ulcer [11]. Theoretically, hydroxocobalamin have several advantages due to better tissue retention and storage as demonstrated in some studies [12]. To our knowledge, it does seem not so evident in clinical practice.

However, despite ancient use, the management concerning both the dose and schedule of administration varies considerably between countries [10]. This fact is related to the lack of randomized study fulfilled the criteria of evidence based-medicine in this field of medicine. In the USA and UK, doses ranging from 100 to 1,000 µg (0.1 to 1 mg) *per* month (or every 2-3 months when hydroxocobalamin is given) are used for the duration of the patient's life [11]. In France, treatment involves the administration of 1,000 µg (1 mg) of cyanocobalamin *per* day for 1 week, followed by 1,000 µg (1 mg) *per* week for 1 month, followed by 1,000 µg (1 mg) *per* month, again, normally for the remainder of the patient's lifetime [10].

Oral vitamin B12 treatment

Since cobalamin is absorbed by intrinsic factor-independent passive diffusion, daily high-dose (pharmacological dose, 1,000 to 2,000 µg [1 to 2 mg] *per* day) oral vitamin B12 (cyanocobalamin) can induce and maintain remission in patients with megaloblastic anemia [3,13]. In

fact, as we have seen before, 1 to 5% of oral vitamin B12 is absorbed through passive way [4]. In this setting, alternative routes of cobalamin administration have been developed, experimented and used with good effect such as the oral [3,10,13] and nasal [14,15]. These other routes of administration have been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections (with the need of a nurse) [16,17].

To our knowledge, several narrative reviews, including patients with Biermer's disease, have reported preliminary data of the efficacy of oral vitamin B12 treatment [3,10,18,19]. Although well done methodologically, results of these reviews have remained relatively confidential, without any real change in world practice at the beginning of the 2000's. This practice is however predominant in the Nordic countries. In these countries, curative oral vitamin B12 treatment accounts for more than 70% of the total vitamin B12 prescribed in Sweden since the 1980s [20].

Nevertheless, to date, with the dissemination of knowledge (through the *Web*) and thanks to the existence of good quality studies, this is changing. Thus, at least four studies that fulfilled the criteria of evidence based-medicine (randomized study, systematic review) supported the efficacy of oral vitamin B12 therapy [21-24]. In the literature, several other recent not randomized studies support the efficacy or oral vitamin B12 replacement [10,17].

Randomized controlled studies of oral vitamin B12 therapy in vitamin B12 deficiency

Several prospective randomized controlled studies comparing oral vitamin B12 *vs.* IM vitamin B12 treatment have well-documented the efficacy (defined as the normalization and or a significant increase of the serum vitamin B12 level) and safety of oral vitamin B12 as a curative treatment [20,21,24]. Three of these currently published prospective studies include at least patients with potential Biermer's disease (n=18). It is to note that the treatment regime of vitamin B12 (frequency and daily dose) the oral and IM groups varied in these studies. To our knowledge, only 2 of the randomized studies have well-documented the efficacy of oral vitamin B12 therapy in term of serum vitamin B12 levels (Table 2) [21,22]. Moreover only 2 studies reported data on adverse events.

In a first study, Kuzminski *et al.* in a prospective randomized trial including 38 patients (7 with pernicious anemia [18,4%]), have reported improvement of hematological parameters and vitamin B12 levels (mean value: 907 pg/mL), after 4 months of oral cyanocobalamin replacement using a much higher dose (i.e. 2,000 µg [2 mg] *per* day) (Table 2) [21]. In this study, serum vitamin B12 levels were significantly higher in the oral (2000 µg [2 mg] of vitamin B12) compared with IM (1000 µg [1 mg] of vitamin B12) group at 2 months: 643 ± 328 *vs.* 306 ± 118 pg/mL; *p* <0.001. The difference was even greater at 4 months: 1005 ± 595 *vs.* 325 ± 165 pg/mL. Four of the 18 patients in the oral group and

Table 2. Prospective randomized controlled studies of oral vitamin B12 treatment in patients with vitamin B12 deficiency, including patients with Biermer's disease [21,22]

Study characteristics (number of patients)	Therapeutic modalities	Results
Prospective randomized controlled study n=38, including 7 patients with Biermer's disease [21]	Oral crystalline cyanocobalamin: 2,000 µg (2 mg) *per* day, during at least 4 months	The mean pretreatment values for serum cobalamin, methylmalonic acid, and homocysteine were, respectively, 93 pg/mL, 3,850 nmol/L, and 37. 2 µmol/L in the oral group and 95 pg/mL, 3,630 nmol/L, and 40.0 µmol/L in the parenteral therapy group. After 4 months of therapy, the respective mean values were 1,005 pg/mL, 169 nmol/L, and 10.6 µmol/L in the oral group and 325 pg/mL, 265 nmol/L, and 12.2 µmol/L in the parenteral group (IM). The higher serum cobalamin and lower serum methylmalonic acid levels at 4 months posttreatment in the oral group *vs.* the parenteral group were significant, with $p<0.0005$ and $p<0.05$, respectively. Correction of hematological and neurological abnormalities was prompt and indistinguishable between the 2 groups
Prospective randomized open-label study, n=60, including 7 patients with Biermer's disease [22]	Oral crystalline cyanocobalamin: at a daily dose of 1,000 µg (1 mg) for 10 days (oral group) or cobalamin IM: 1,000 µg (1 mg) once daily for 10 days (IM group). After 10 days, both treatments were administered once a week for 4 weeks, and after that, once a month for life	The mean serum vitamin B12 concentration increased significantly from day 0 to 90 ($p<0.001$). In the oral group, at days 30 and 90, all hematological parameters changed significantly *vs.* day 0 (mean hemoglobin levels increased [both $p<0.001$]; mean corpuscular volume decreased [both $p<0.001$]; mean white blood cell count increased [day 30, $p<0.01$; day 90, $p<0.001$]; and mean platelet count increased [both $p<0.001$]). Reticulocytosis was observed in all patients. These hematological parameters and the recovery patterns were similar between the 2 groups. Neurological improvement was detected in 78% in the oral group and 75% in the IM group at day 30

4 of the 15 in the IM group had a neurological response with a marked improvement or clearing of paresthesia, ataxia, or memory loss.

Bolaman *et al.* in a prospective randomized trial of 60 patients (11 with pernicious anemia [18,3%]), also reported significant improvement of hematological parameters and vitamin B12 levels (mean improvement: +140.9 pg/mL), after 3 months of daily 1,000 µg (1 mg) of oral cyanocobalamin therapy (Table 2) [22]. In this study, there was an increase in serum vitamin B12 levels in both groups (1000 µg [1 mg] of oral vitamin B12 *vs.* 1000 µg [1 mg] of IM vitamin B12) at 90 days: 213.8 pg/mL in the oral and 225.5 pg/mL in the IM group. There was a statistically significant difference between days 0 and 90 in both groups ($p<0.0001$), but authors did not analyze difference between both groups. Both groups reported improvements of cognitive functions, sensory neuropathy, and vibration sense, but there was no statistically significant difference between both groups.

In a recent controlled, randomized, multicenter, parallel, non-inferiority clinical trial lasting one year, a preliminary analysis gives a glimpse that the oral route may be as effective and safety and more cheaply than the IM route [25]. This study involves 23 primary healthcare centers in the Madrid region (Spain), and 320 patients ≥65 years of age. In this study, IM vitamin B12 will be administered as follows: 1,000 µg (1 mg) on alternate days in weeks 1 and 2, 1,000 µg (1 mg) *per* week in weeks 3-8, and 1,000 µg (1 mg) *per* month in weeks 9-52. In the oral arm, the vitamin B12 will be administered as: 1,000 µg (1 mg) *per* day in weeks 1-8 and 1,000 µg (1 mg) *per* week in weeks 9-52. The definitive results of the Project *OB12* study are expected for 2020.

In another randomized, parallel-group, double-blind, dose-finding trial, Eussen *et al.* showed that the lowest dose of oral cyanocobalamin required to normalize mild vitamin B12 deficiency is more than 200 times the recommended dietary allowance of approximately 3 µg daily (i.e. >500 µg [0.5 mg] *per* day) [24]. No data of the cobalamin deficiency etiology is available. Apart from helping to determine the dose, this study gives no indication for the Practitioners of the clinical effectiveness of oral vitamin B12 treatment.

It is to note that in the above studies explored the regression of the clinical manifestations (especially neurological signs) there was no relevant difference in the efficacy of oral or IM vitamin B12 administration [21,22,24]. Nevertheless, to our knowledge, the effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented. Thus, until this has been studied, parenteral vitamin B12 therapy is still to be recommended for such patients [26].

To our knowledge, 2 of the aforementioned studies reported data on adverse events, with 2 of such adverse events in one study in the group of oral vitamins B12 [21,22].

Systematic reviews of oral vitamin B12 therapy in vitamin B12 deficiency

The first evidence-based analysis by the *Vitamin B12 Cochrane Group* in 2005 supports the efficacy of oral vitamin B12 as a curative treatment, with a dose between 1,000 and 2,000 µg (1 and 2 mg) initially prescribed daily and then weekly [27]. This structured-analysis includes patients with Biermer's disease. In this analysis, serum vitamin B12 levels increased significantly in patients receiving oral vitamin B12 and both groups of patients (receiving oral and IM treatment) showed an improvement in neurological symptoms. The *Cochrane Group* concludes that daily oral therapy may be as effective as IM administration in obtaining short term hematological and neurological responses in vitamin B12 deficient patients [27].

The recent evidence based-analysis from the same group in 2018, also including the context of Biermer's disease, confirms their previous analysis [23]. In fact, the *Cochrane Group* concludes that: "*there is evidence of low quality that oral vitamin B12 or vitamin B12 administered intramuscularly have similar effects in normalizing vitamin B12 serum levels, but oral treatment costs less. Further trials should conduct better randomization and blinding procedures, recruit more participants, and provide adequate reporting. Future trials should also measure important outcomes such as the clinical signs and symptoms of vitamin B12 deficiency, health related-quality of life, socioeconomic effects, and report adverse events adequately*".

Prospective studies of oral vitamin B12 therapy in patients with Biermer's disease

Our working *CARE B12* group has developed an effective oral curative treatment for patients presenting with FCM and pernicious anemia using crystalline cyanocobalamin [28-32]. This treatment has been validated through several studies on small numbers of patients with a well-documented vitamin B12 deficiency, this latter of well-defined etiology. In the majority of studies, the effectiveness of treatment has been validated on the correction of serum vitamin B12 levels and that of hematological abnormalities, in general at 3 months (short term efficacy) [28-32]. In some studies, correction of neurological signs or clinical manifestations has also been sought. In all the studies, adverse events were studied.

Analysis of these data from the studies conducted by the *CARE B12* group confirms the previously reported efficacy of oral crystalline cyanocobalamin, particularly in FCM and in elderly patients [28-31]. All of the patients who were treated orally corrected their vitamin B12 levels and at least two-thirds corrected their hematological abnormalities. Moreover, one-third of patients experienced a clinical improvement on oral treatment. In most cases of FCM a low vitamin B12 dose (i.e. 125–1,000 µg [0.125 to 1 mg] of oral crystalline cyanocobalamin *per* day) was used.

The aforementioned results were also observed in a population of patients presenting with Biermer's disease (Table 3) [33]. In this setting, the *CARE B12* group studied in an open study 10 patients with well-documented vitamin B12 deficiency related to pernicious anemia who daily received 1,000 µg (1 mg) of oral crystalline cyanocobalamin for at least 3 months [32]. After 3 months of treatment, serum vitamin B12 levels were increased in all 9 patients in whom it was measured (mean increase of 117.4 pg/mL; *p* <0.0000003 compared with baseline). Eight patients had increased hemoglobin levels (mean increase of 2.45 g/dL; *p* <0.01). All 10 patients had decreased mean erythrocyte cell volume (mean decrease of 10.4 fL; *p* <0.003). Three patients (one-third) experienced clinical improvements.

Two other studies have documented the efficacy of oral vitamin B12 therapy in patients with pernicious anemia (Table 3) [20,34]. These studies also had small sample size but had longer follow-up period (up to 18 months).

Oral vitamin B12 was effective in all the patients (10 patients had Biermer's disaese) in Nyholm's study (n=40) with the median serum vitamin B12 level of 1,193 pg/mL after 3 months of treatment (Table 3) [20]. It was also reported that using oral treatment did not result in any new neurological complications.

Normalization of serum vitamin B12 levels was seen in all patients (inclusive of patients with pernicious anemia) in Delpre's study with oral (sublingual) vitamin B12 replacement (n=18) (Table 3) [34]. An increase in vitamin B12 level was as much as fourfold compared with pretreatment in most patients. The mean change of 387.7 pg/mL was significant (*p*=0.0001).

The *CARE B12* group had also documented the long-term efficacy of oral vitamin B12 treatment, with a median follow up of 2.5 years, in a population of 22 patients including patients with pernicious anemia

[35]. These preliminary findings are in accordance with the results of Roth's study, with a median follow up of more than 4 years on oral vitamin B12 therapy [36].

The *CARE B12* group also documented in a small study (10 patients) the relative efficacy of oral cyanocobalamin treatment on cognitive functions (Mini Mental State Examination score) [37].

In these studies, including 132 patients [28-32], only 2 of these (1.5%) reported treatment-related adverse events such as skin allergy.

Experience of oral vitamin B12 therapy in patients with Biermer's disease in a reference center

Thus, since the 2000's, at least half of the patients followed in the *Hôpitaux Universitaires de Strasbourg* (University Hospital of Strasbourg, Strasbourg, France) with well-documented vitamin B12 deficiency were treated with oral cyanocobalamin, with a dose between 125 and 2,000 µg (0.125 to 2 mg) *per* day depending on whether the cause is Biermer's disease or FCM (Table 4 for the used scheme) [26]. In the Department of Internal Medicine in the aforementioned Institution (>800 patients with a documented cobalamin deficiency, median age 71 years), FCM accounts for about 60–70% of the cases of vitamin B12 deficiency in elderly patients, whereas Biermer's disease accounted for only 15–25% [38]. All of these patients who were treated orally corrected their vitamin B12 levels and at least 80% corrected their hematological abnormalities [26]. Moreover, half of the patients experienced a clinical improvement on oral treatment. It is to note that the patients presenting with severe neurological manifestations were usually excluded by our team for the oral vitamin B12 treatment. In the experience of the *CARE B12* group, oral vitamin B12 treatment avoids the discomfort, inconvenience and cost of monthly injections.

Perspectives and direction of future research

To date the oral vitamin B12 treatment regimen not yet formally approved [3]. Further studies should include testing the efficacy of different molecules (cyano-, hydroxo-, methyl-cobalamin) and dosages. It may be important to study the knowledge and practices of doctors/health-care workers with regard to oral replacement therapy with vitamin B12 for patients with cobalamin deficiency.

Recent developments in conjunction with nanomedicine for the co-administration of drugs with lipid compounds have been reported

Table 3. Studies of oral vitamin B12 treatment in patients with Biermer's disease [20,32,34,35]

Study characteristics (number of patients)	Therapeutic modalities	Results
Prospective, case series of low vitamin B12 levels (n=40), including 10 patients with Biermer's disease [20]	Loading dose of IM vitamin B12 till vitamin B12 level reached lower 25th centile (418 pg/mL) and then converted to oral vitamin B12 1000 µg (1 mg) *per* day, during 3–18 months	Normalization of the serum vitamin B12 levels in all patients. At 3 months, median serum vitamin B12 level of 1193 pg/mL No adverse-effect
Open prospective study of low vitamin B12 levels related to Biermer's disease (n=10) [32]	Oral crystalline cyanocobalamin: 1,000 µg (1 mg) *per* day, during at least 3 months	Significant increase of serum vitamin B12 levels in 90% of the patients (mean of 117.4 pg/mL Significant increase of Hb levels (mean of 2.45 g/dL) and decrease of ECV (mean of 10.4 fL) Improvement of clinical abnormalities in 30% of the patients No adverse-effect
Open prospective study of low vitamin B12 levels related to Biermer's disease (n=18) [34]	Sublingual cobalamin for 7–12 days	Normalization of serum vitamin B12 levels. Significant mean changes of 387.7 pg/mL (*p*=0.0001) Increase in vitamin B12 level as much as fourfold compared with pretreatment in most patients
Cohort study of low vitamin B12 levels (n=22), including patients with Biermer's disease [35]	Oral crystalline cyanocobalamin: 650 µg (0.65 mg) *per* day, during a median of 2.5 years	Normalization of serum vitamin B12 levels in 95% of the patients Significant increase of Hb levels (mean of 1.1 g/dL) Improvement of clinical abnormalities in 20% of the patients No adverse-effect

Hb: Hemoglobin; ECV: Erythrocyte cell volume; MMSE: Mini mental state examination

Table 4. Recommendations for oral vitamin B12 treatment [23,26]

	Biermer's disease	Intake deficiency and food-cobalamin malabsorption
Parenteral administration (intramuscular)	Cyanocobalamin: - 1,000 µg (1 mg) *per* day for 1 week - than 1,000 µg (1 mg) *per* week for 1 month - than 1,000 µg (1 mg) *per* each month, for life (1,000 to 2,000 µg [1 to 2 mg] *per* day for at least 1 to 3 months in case of severe neurological manifestations)	Cyanocobalamin: - 1,000 µg (1 mg) *per* day for 1 week - than 1,000 µg (1 mg) *per* week for 1 month - than 1,000 µg (1 mg) *per* each 1 or 3 months, until the cobalamin deficiency cause is corrected (1,000 µg [1 mg] *per* day for at least 1 to 3 months in case of severe neurological manifestations)
Oral administration	Cyanocobalamin: 1,000 µg (1 mg) *per* day for life*	Cyanocobalamin: - 1,000 µg (1 mg) *per* day for 1 month - than 125 to 1,000 *µg* (0.125 to 1 mg) *per* day, until the cobalamin deficiency cause is corrected*

*The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

to enhance lymphatic transport. These technologies have been recently used to administrate vitamin B12 [39].

Nasal and sublingual administrations of vitamin B12 (placing the vitamin beneath the tongue for one to two minutes) are another promising way of administration that are studied [14,34].

Conclusions and recommendations

To date in worldwide clinical practice, the majority of patients with vitamin B12 deficiency is treated with parenteral vitamin B12 administration. In fact, several studies in 2000s have documented that lifelong IM injection for replacement is still a common and usual practice. Nevertheless, as early as the 1950s, there were studies suggesting that oral vitamin B12 replacement may provide adequate absorption. Nevertheless, oral vitamin B12 replacement in patients with vitamin B12 remains uncommon in clinical practice. In this setting, oral cobalamin remains the "*best keep secret in medicine*" [40]. In our opinion, it may be "*time to communicate on this treatment possibility*" and "*time to propose international recommendations*" [41].

The present analysis and the experience of the *CARE B12* group support the use of oral vitamin B12 replacement in clinical practice. Considering the present work, we can recommend a dose of 1,000 µg (1 mg) *per* day of oral cyanocobalamin for life in case of Biermer's disease (Table 4) [23,26]. In case of intake deficiency or food-cobalamin malabsorption, we can recommend 1,000 µg (1 mg) *per* day of oral cyanocobalamin for 1 month and then 125 to 1,000 µg (0.125 to 1 mg) *per* day, until the cobalamin deficiency cause is corrected. In this setting, the following can also be proposed: ongoing supplementation is needed until any associated disorders are corrected (e.g. by halting the ingestion of the offending medication or exogenesis, or by treating *Helicobacter pylori* infection or pancreatic exocrine failure) [9,26]. This may result in lifelong administration or, when applicable, sequential administration.

The effect of oral vitamin B12 treatment in patients presenting with severe neurological manifestations (e.g. combined sclerosis) has not yet been adequately documented [23,26]. Thus, such patients with should be treated with IM replacement, to favor rapid replenishment of vitamin B12 stores and to avoid irreversible consequences of the vitamin deficiency. After major regression of the manifestation, patients may be able to be treated with oral vitamin B12 replacement (required a close monitoring).

In clinical practice, one of the predominant elements for the choice of treatment options is the patient preference [26,42]. This latter should absolutely be taken into consideration. Other factors of this choice (IM *vs.* oral) include patient compliance and patient comorbidities. Thus, in patients with non-compliance to oral vitamin B12 treatment,

IM vitamin replacement may be a better option. In patients, whereby IM injections are contraindicated because of coagulopathy or the use anti-coagulation and/or anti-platelet medication, oral replacement is the best option. In this setting, oral replacement will also be interest to avoid painful and administration difficulties.

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Competing interests

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

Authors contribution

Conceived and designed the study: EA and AAZ. Performed the study: EA, AAZ and TV. Analyzed the data: EA and AAZ. Interpreted the results: EA and AAZ. Wrote the paper: EA and AAZ. Principal Investigator of this study and supervised this study: EA. Revised the paper critically and give final approval for publication: all authors.

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