Thrombopoietic Factors in Chronic Bone Marrow Failure States: The Platelet Problem Revisited

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ABSTRACT
Thrombocytopenia is a serious clinical problem in several different clinical settings. In chronic bone marrow failure states, which include aplastic anemia, myelodysplastic syndrome, and graft failure, the prolonged nature of thrombocytopenia often leads to alloimmunization after repeated platelet transfusions, the consequence of which is a platelet-refractory state and enhanced risk of bleeding. Despite the introduction of several thrombopoietic factors into clinical trials, an effective way to alleviate thrombocytopenia has been elusive, and the problem in chronic bone marrow failure states has remained poorly addressed by clinical investigations. Even so, several studies by our group and others suggest that a subset of patients suffering from chronic bone marrow failure can respond to appropriate growth factor therapy. The temporal pace of response appears, however, to be much slower than that observed after administering growth factors which act on neutrophils. On the other hand, durable responses can be secured in some patients given thrombopoietic factors for long periods of time. Herein, we provide an overview of the clinical research investigations of thrombopoietic factors in chronic bone marrow failure, and the emerging insights these studies provide for understanding the process of thrombopoiesis and its therapy in this setting.

BACKGROUND
Chronic bone marrow failure is a pre-eminent feature of several disorders including, but not limited to, aplastic anemia, myelodysplastic syndrome, and graft failure. Occasionally, patients also suffer from prolonged cytopenias after chemotherapy or radiation therapy. The etiology of bone marrow failure in each of the above conditions covers the spectrum from idiopathic to toxins (environmental or iatrogenically-introduced) and viral insults, as well as the presence of pre-leukemic clones.

Patients with bone marrow failure suffer from neutropenia and thrombocytopenia resulting in increased infections and a propensity to bleeding, respectively. In addition, anemia leads to fatigue and loss of quality of life. Anemia may also strain cardiac and neurologic function, and recent studies suggest a negative impact on survival (1). Affected patients often have limited treatment options.

Hematopoietic progenitor cell proliferation and differentiation are largely regulated by acidic lipoproteins known as hematopoietic growth factors or colony stimulating factors (2). Because of their biology, bone marrow failure states represent a natural venue for evaluating the efficacy of these growth factors. However, clinical investigation of growth factors has been carried out mainly in patients undergoing chemotherapy or transplantation. The number of trials using growth factors in bone marrow failure states is relatively small, and clinically meaningful multilineage or thrombopoietic responses have been elusive. Even so, several studies by our group and others have shown that subsets of such patients will respond to a variety of growth factor regimens (3–5). Herein, we review clinical studies of thrombopoietic factors in chronic bone marrow failure settings, and the insights that these studies provide into the biology of thrombopoiesis and the treatment of thrombocytopenia.

HISTORICAL PERSPECTIVE
Starting in the late 1980s, the introduction of recombinant growth factors into the clinic heralded a revolution in our ability to treat neutropenia and anemia (6–9). Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) result in consistent increases in white blood cell (WBC) count and a decrease in infectious episodes in a variety of clinical conditions, and have been widely adopted in the post-chemotherapy or post-transplant setting (10). In bone marrow failure states, impact on infection and survival is less clear cut, but these molecules consistently increase WBC count (10). Because they act on relatively mature cells, responses often occur within 24 hours; however, drug withdrawal is accompanied by a rapid drop in blood counts to baseline values. Recently, a pegylated version of G-CSF (Neulasta) has been approved (11). The slow clearance of this drug prolongs its action, and only a single dose is required after chemotherapy. Its effects in bone marrow failure have not yet been well established.

Strides in the treatment of anemia with growth factors have also been significant. Erythropoietin (EPO) is particularly effective in patients with renal failure (12). In this condition, the kidney, being a key source of EPO, fails to produce adequate amounts of this molecule, resulting in low circulating levels. Administration of erythropoietin, or a newer form of this molecule with prolonged action (darbepoietin alpha) (13), acts as replacement therapy. Patients with anemia due to cancer or
therapy also respond to erythropoietin to variable extents (14). Treatment of anemia is associated with improved quality of life, though effects on survival are controversial (15, 16). In bone marrow failure states, production of EPO by the kidney remains intact, and circulating EPO levels are high. As a result, only a subset of patients respond to exogenous administration of pharmacological doses of EPO (17).

The problem of thrombocytopenia has remained the most recalcitrant. A series of thrombopoietic factors—interleukin-3 (IL-3), IL-9, IL-1β, stem cell factor (SCF), and thrombopoietin (TPO) have been introduced to the clinic, and each in its turn has been touted for its preclinical thrombopoietic activity. Unfortunately, very limited platelet recovery is observed in the patient care setting. Only IL-11 attained Federal Drug Administration approval in the U.S.; its indication is post-chemotherapy thrombocytopenia.

Overall, a paucity of studies exists in bone marrow failure. Furthermore, the studies that do exist suggest that hematopoietic growth factor therapy of these conditions is not straightforward. Nevertheless, amelioration of anemia, neutropenia, and thrombocytopenia is possible in some patients, and even durable, multilineage responses have been reported (4, 5).

WHY IS THROMBOCYTOPENIA IMPORTANT?

Thrombocytopenia is a significant, unresolved clinical problem, especially in patients with chronic bone marrow failure. Each year in the United States, millions of units of platelets are transfused into patients to reduce the risk of severe bleeding. However, platelet transfusions are far from ideal. Complications include febrile reactions and, less commonly, bacteremia. In about one-fifth of individuals who require repeated platelet transfusions, incremental platelet responses are inadequate as a result of alloimmunization. Finally, platelet transfusions are expensive.

WHAT DO WE KNOW ABOUT MEGALOCYOCYTE DEVELOPMENT?

Hematopoietic stem cells ultimately give rise to all the formed elements of the blood: mature lymphocytes, granulocytes, monocytes, erythrocytes, and megakaryocytes. This process of cellular proliferation and differentiation requires the support of several interleukins, colony-stimulating factors, and hormones. In general, two or more of these proteins are required for each hematopoietic lineage to fulfill its developmental potential. Despite this redundancy, distinct factors supporting the same lineage have actions that differ in subtle but critical ways (reviewed in ref. 18).

The development of megakaryocytes requires several cytokines. Early-acting molecules include IL-3 as well as SCF. TPO has several pivotal actions during megakaryopoiesis. It increases the size and number of megakaryocytes, stimulates their expression of platelet-specific markers, promotes endomitosis and megakaryocyte polyploidy, acts to induce megakaryocyte colony formation, and synergizes with other thrombopoietic molecules (including IL-3, IL-11, SCF, and EPO). Of interest, TPO also acts in concert with EPO to stimulate the growth of erythroid progenitor cells, and with IL-3 or SCF to promote the proliferation and prolong the survival of hematopoietic progenitors.

In summary, many stages of megakaryocyte development can be affected by a series of cytokines in vitro. These cytokines include SCF, IL-3, IL-6, IL-11, G-CSF, EPO, leukemia inhibitory factor, and TPO. Although the interplay of these cytokines supports various aspects of megakaryocyte development in vitro, it is only genetic eradication of SCF or TPO which severely impacts megakaryocyte and platelet production in animal models (reviewed in ref. 18). Whether or not these results can be extrapolated to humans is unclear.

HEMATOPOIETINS WITH THROMBOPOIETIC ACTIVITY IN THE CLINIC

Several molecules with putative thrombopoietic activity have entered the clinic (Table 1). These molecules include IL-3, IL-6, IL-11, stem cell factor (SCR) and thrombopoietin (TPO).

- IL-11 is a thrombopoietic cytokine that promotes the growth of hematopoietic stem cells and megakaryocytic progenitors. It induces megakaryocyte differentiation in vitro and results in increased platelet counts in animal models of compromised hematopoiesis (18–21). IL-11 administered to mice undergoing bone marrow transplantation after total-body irradiation stimulates platelet and neutrophil recovery (19, 20). When stem cell factor is also given, increases in all three lineages without toxicity is observed (19).

- In humans, several studies have demonstrated that IL-11 attenuates chemotherapy-induced thrombocytopenia (22, 23). Its approved use is specific for this indication. After chemotherapy, it is given for 5-7 days at a dose of 50 μg/kg/day s.c. Randomized studies have found that platelet nadirs are not as low with this treatment (22, 23).

We recently performed a study of low-dose IL-11 in patients suffering from bone marrow failure (3). Our initial experience suggested that the 50 μg/kg/day dose used for one week or less after chemotherapy was not tolerable in this setting.

### Table 1: Molecules with potential thrombopoietin activity

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Interleukin-11</td>
<td>FDA-approved in U.S. for postchemotherapy thrombocytopenia</td>
</tr>
<tr>
<td>Interleukin-3</td>
<td></td>
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<tr>
<td>Interleukin-6</td>
<td>Approved in Canada, New Zealand, and Australia for stem cell mobilization</td>
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<tr>
<td>Stem cell factor</td>
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<tr>
<td>Thrombopoietin</td>
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<tr>
<td>GM-CSF/IL-3 fusion protein</td>
<td>PIXY321</td>
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<tr>
<td>Dual IL-3/TPO receptor agonist</td>
<td>Promegapoietin-1a</td>
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<tr>
<td>Dual G-CSF/IL-3 receptor agonist</td>
<td>Leridistin</td>
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<tr>
<td>Interleukin-3 receptor agonist</td>
<td>Daniplestin</td>
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most likely because of the prolonged, continuous administration required. Indeed, after two weeks of daily administration, side effects included substantial pulmonary and peripheral fluid accumulation. Early exploration of decreasing dose levels suggested that IL-11 needed to be reduced to 10 μg/kg/day s.c. on alternate days or daily in order to be acceptable to patients. At this dose level, half of the patients have no side effects and the others have only mild toxicities, generally related to fluid retention in the lower extremities (3). After receiving low-dose IL-11, about 40% of patients with bone marrow failure demonstrated platelet responses, with the median increase in platelet counts being 95 × 10^3/μl above baseline (3). The time to initial platelet response was usually two to four weeks, but could be as long as four months. Multilineage responses were also observed with either IL-11 alone or with a combination of IL-11, EPO and G-CSF.

Multilineage response to IL-11 alone may be mediated through any one of several mechanisms. In particular, IL-11 can stimulate multilineage progenitors in in vitro models (18). Alternatively, it is theoretically possible that, in MDS, IL-11 has some antitumor activity. The latter notion is supported by observations suggesting that IL-11 suppresses production of cytokines (such as tumor necrosis factor-alpha) that have been implicated in certain leukemic processes (24, 25). In addition, in a recent, small, randomized clinical study of patients with acute myelogenous leukemia given gemtuzumab ozogamicin (which targets the myeloid marker CD33) either with or without IL-11, a statistically significant increase in remission rate was achieved in the arm receiving IL-11 (26).

**IL-3**

Clinical studies using IL-3 alone in bone marrow failure have shown only limited efficacy (27–30). In our study in a broad spectrum of bone marrow failure states, modest increases in neutrophils were observed in about one-third of patients; platelet responses occurred anecdotally and were generally minor in nature (27). IL-3 therapy in patients with MDS, HIV-associated cytopenias, and congenital amegakaryocytic thrombocytopenia have also shown only modest results. Hemoglobin and platelet rises are seen in a small minority of individuals and the overall effect of IL-3 on neturophil, platelet or hematocrit recovery has been disappointing (31–33). At higher doses, eosinophilia occurs (32). Cytogenetic and molecular analysis using restriction fragment length polymorphism (RFLP) indicated that, in MDS, both the malignant cell clone and normal cells were stimulated to the same extent (34). The risk of transformation remains a theoretical concern. However, among large groups of patients, less than 5% experience an increase in blast cells during IL-3 treatment or shortly thereafter (35, 36). In most of these individuals, the blasts fall to baseline shortly after stopping IL-3 (27). IL-3 has also been used in an effort to correct erythropoiesis in constitutional, pure red blood cell aplasia (Diamond-Blackfan anemia). A subset of steroid-responsive patients may achieve sustained remission (37) but most patients are unresponsive (38). The role of IL-3 alone or combined with other cytokines has also been assessed in cases with delayed engraftment following autologous bone marrow transplant. No improvement was seen (39). However, only 21 days of IL-3 were administered in this study.

Because preclinical studies of IL-3 suggest that the effects of this molecule requires the concomitant presence of additional growth factors, several investigators have administered IL-3 together with other hematopoietins. Studies of sequential IL-3 followed by GM-CSF were based on monkey studies supporting synergy for this regimen. Very little clinical benefit is seen at IL-3 doses less than 1.0 μg/kg/day (5, 40). However, at higher doses, one-third of patients had platelet responses, and 21% had multilineage responses (5). Interestingly, all platelet responders also had a hemoglobin response despite the fact that EPO was not administered. Platelet responses were initially seen after 1 to 12 weeks of therapy, and maximal responses were reached after one year or more of treatment. Furthermore, for patients who were treated for over one to two years and achieved full hematologic recovery, remissions remain durable and ongoing even several years after drug withdrawal (5). Interestingly, IL-3 has also been demonstrated to “prime” the bone marrow, so that in a patient with aplastic anemia previously unresponsive to G-CSF, pretreatment with IL-3 followed by a course of G-CSF resulted in a neutrophil response (41). The latter results are consistent with those in primate models which demonstrate that pretreatment with IL-3 potentiates the effects of GM-CSF on myelopoiesis, of EPO on erythropoiesis, and of IL-6 on thrombopoiesis (42–44).

**IL-6**

IL-6 is a pleiotropic cytokine with diverse activities that include the ability to stimulate B-cell differentiation to augment the generation of cytotoxic T lymphocytes (45) and to induce acute phase protein including C-reactive protein, fibrinogen, and α2-microglobulin (46). IL-6 enhances the in vitro effects of IL-3 on hematopoietic progenitor cells and promotes the maturation of megakaryocyte precursors, thus stimulating thrombopoiesis (47–51). Preclinical animal data in mice and nonhuman primates have demonstrated that IL-6 has potent thrombopoietic activity (52, 53).

To evaluate the hematologic effects of recombinant human IL-6 and determine its toxicity profile, a phase I trial of IL-6 in 22 patients with myelodysplastic syndromes was performed (54). Patients received one of four doses of IL-6 (1.0, 2.5, 3.75, and 5.0 μg/kg/d) as a subcutaneous injection on day 1, followed by a 7-day wash-out period, and then 28 days of IL-6 therapy. Dose-limiting toxicities of fatigue, fever, and elevated alkaline phosphatase were seen at 5.0 μg/kg/d; the maximum tolerated dose was 3.75 μg/kg/d. All patients experienced at least grade II fever and all had an increase in acute phase proteins. Three patients fulfilled the criteria for response, whereas five others had clinically significant increases that failed to meet response criteria. Various IL-6–related toxicities prevented several patients from receiving maintenance therapy. Two of the three patients who received maintenance IL-6 therapy had a persistent increase in platelet counts, during 3 and 12 months of IL-6 therapy, respectively. Laboratory studies indicated that IL-6 increased the frequency of higher ploidy megakaryocytes, but did not significantly increase the number of assayable megakaryocytic progenitor cells, suggesting that IL-6 acts as a maturational agent rather than a megakaryocyte colony-stimulating factor. A synthesis of this study indicates that IL-6 therapy can promote thrombopoiesis in some MDS patients, but
its limited activity and significant therapy-related toxicity preclude its use as a single agent in this patient population.

Stem Cell Factor

Stem cell factor (SCF) is also known as kit ligand, mast cell growth factor, or steel factor. It functions as a hematopoietic cytokine that triggers its biologic effect via binding to c-kit (55, 56). SCF is constitutively produced by marrow stromal elements. It is now well established that SCF acts on hematopoietic stem cells and, in some lineages, mature cells.

SCF synergizes with other cytokines (including EPO, IL-3, GM-CSF, and G-CSF) to support the direct colony growth of burst forming units-erythroid (BFU-E), colony forming units—granulocyte macrophage (CFU-GM), and CFU-granulocyte/erythroid/macrophage/megakaryocyte (GEMM) in semisolid media, and current data suggest that SCF can act on a more primitive cell (56). SCF can also promote progenitor cell survival, accelerate stem cell entry into cell cycle, and function as a chemotactic and chemokinetic factor for these cells. Synergistic proliferative effects on megakaryocytic progenitor cells are observed when SCF is combined with thrombopoietin (TPO) or IL-3 (57).

A Phase I study of SCF in aplastic anemia has been performed. Patients who were severely neutropenic also received G-CSF (4). Multilineage responses were seen in 17% of patients treated at dose levels ≥25 μg/kg s.c. three times per week, but in only about 5% of patients treated with lower doses. Patients who received SCF alone (without G-CSF) also responded. Of interest, the median time to initial evidence of response was four months, and maximal response was generally reached after over one year of therapy. In patients who discontinued therapy early after response was achieved (i.e., after only several months and while platelet counts were still rising), platelet counts fell to baseline, albeit gradually over a period of months. In some patients who were treated for prolonged periods (over two years) with normalization or near-normalization of counts, responses were maintained after SCF discontinuation for periods ranging from 1.5 years to ongoing remissions at 3 years. This study suggests that prolonged SCF administration, either alone or with G-CSF, can induce durable, multilineage remissions in patients with moderate to severe aplastic anemia.

Thrombopoietin

Thrombopoietin (TPO) is the ligand for c-mpl (the TPO receptor) and is a key cytokine regulating megakaryocytopoiesis (58–72). It is mostly produced in the liver (60, 61). The TPO receptor is expressed on platelets and megakaryocytes. After binding to mpl, TPO is internalized and metabolized, resulting in the elimination of the cytokine (62). TPO serum levels are thus regulated by platelet and megakaryocyte mass (62). The finding that platelets can remove TPO from the circulation suggests that platelet transfusions may blunt megakaryocyte recovery. Of interest, mutations in the TPO receptor (mpl) have been found in children with congenital amegakaryocytic thrombocytopenia. Since these children can also suffer from bone marrow failure, it appears that mpl may influence not only megakaryocyte formation, but also stem cell survival (71).

In animal models of myelosuppression, the administration of recombinant TPO reduces severity and duration of thrombocytopenia (63, 64). Administration of recombinant TPO to patients with normal marrow function increases platelet counts and megakaryocyte marrow content (65, 66). Giving TPO after chemotherapy results in a higher nadir and a shorter time to recovery of platelet count (67, 68). However, one form of TPO (PEG-rHuMGDF) has been abandoned because of the induction of anti-TPO antibodies resulting in worsening thrombocytopenia (69).

Based on the data from preclinical and early clinical studies, a phase I study was conducted to evaluate the safety of and responses to TPO as treatment for delayed platelet recovery in recipients of stem cell transplants (70). Ten of 37 patients showed platelet recovery. Several design problems confound the interpretation of the data in this study. On the one hand, since patients were treated as early as 35 days after transplant, a period of time within which spontaneous platelet recovery still occurs, the relationship between "response" and TPO administration remains unclear. On the other hand, the ability to stimulate thrombopoiesis may have been underestimated because the schedule of administration was restricted to either one or five doses of TPO per month.

Genetically Engineered Cytokine-Related Molecules

Several recombinant growth factor or growth factor receptor agonists and hybrid agonists have been developed (72–84). They demonstrate significant preclinical activity and encouraging, albeit preliminary, results in clinical trials. For the most part, they have not been tested in bone marrow failure states.

IL-3R Agonist. A genetically engineered, high-affinity IL-3 receptor (IL-3R) agonist (Daniplestim) that exhibits 10 to 20-fold greater hematopoietic activity and minimal inflammatory side effects compared with native and recombinant human IL-3 has been produced (84). Its favorable therapeutic index is due to a 21-amino acid deletion from the N- and C-terminal regions and changed positions of 27 amino acids compared with native IL-3. This change in the IL-3R agonist mediates enhanced binding to the α subunit of the IL-3Rαβ complex (72, 84). Experiments have demonstrated that there is accelerated and improved neutrophil and platelet recovery in rhesus monkeys with synthokine therapy after high-dose chemo-radiotherapy (84).

Chimeric, Dual G-CSF and IL-3 Receptor Agonist. In vitro use of this chimera (SC70935, Leridestim) resulted in enhanced hematopoietic colony formation as compared to IL-3 receptor agonist or G-CSF alone, or to equimolar combinations of the two (73). Enhanced mobilization of hematopoietic progenitors is also promoted by this molecule in non-human primates (74). A phase I/II study of the IL-3R/G-CSF receptor construct in patients with relapsed lymphoma receiving combination chemotherapy has been conducted and demonstrates that it is well tolerated and appears to ameliorate myelosuppression (75).

Dual IL-3 and mpl-L Receptor (TPO Receptor) Agonist (Promegapoeitin-1alpha). Preliminary data demonstrate that this chimeric construct is a potent enhancer of CD34-positive cells and granulocytic and megakaryocytic expansion and, in
non-human primates, it stimulates hematopoietic recovery following radiation-induced myelosuppression (76). GM-CSF/IL-3 Fusion Protein (PIXY321). Complementary in vitro and in vivo effects of GM-CSF and IL-3, combined with their cross competition for common receptor subunit binding, formed the rationale for synthesizing a novel fusion protein, PIXY321, composed of GM-CSF and IL-3 linked by a short amino acid sequence (77). Clinical trials demonstrated biological and clinical activity in adults with normal hematopoiesis as well as in those undergoing peripheral blood stem cell mobilization and recovering from autologous bone marrow transplantation (77–82). In bone marrow failure states, improved absolute neutrophil counts were consistently demonstrated with less predictable responses in other lineage. Trilineage responses were confined to a small number of children who were transfusion independent (83).

**SUMMARY AND FUTURE DIRECTIONS**

The clinical development of thrombopoietic agents has proven challenging, with modest or disappointing results (69). Even so, several trials by our group and others have shown that subsets of patients with bone marrow failure will respond to a variety of growth factor regimens, including low-dose IL-11 (3), stem cell factor (± G-CSF) (ref. 4), and sequential IL-3/GM-CSF (5). With all of these molecules, the temporal relationship between administration and platelet response in bone marrow failure can differ substantially from the rapid response model expected based on the G-CSF/GM-CSF paradigm for white blood cells. Continuous therapy for two weeks to four months is needed before initial evidence of response, and full normalization may require one year or longer (3–5). Furthermore, in contrast to the rapid decline of counts that occurs after withdrawal of G-CSF or GM-CSF, platelet responses appear to be durable for months or years after withdrawal of growth factor. In some studies, platelet responses are accompanied by red cell recovery (even without concomitant EPO administration) and normalization of neutrophils may also occur (both with or without G-CSF and GM-CSF) (ref. 4, 5). Furthermore, a subset of patients can develop durable multilineage responses, which are maintained for months or years after growth factors are discontinued (4, 5).

The fact that the temporal relationship between drug administration and platelet response can be similar, despite the use of several distinct hematopoietins, suggests that this response pattern reflects megakaryocyte/platelet development physiology, and is not necessarily a feature of the molecule administered. In other words, it appears that the expectation that platelets will rise quickly after administration of growth factor, as is seen for neutrophils after G-CSF, may be physiologically unrealistic. Instead, weeks to months of therapy may be necessary. Interestingly, hematologic recovery after administration of antithymocyte globulin to patients with aplastic anemia is delayed by a similar time frame (about three months) (ref. 85). Hence, it is conceivable that some putative thrombopoietic agents may have been designated ineffective in bone marrow failure when, in fact, the short duration of therapy given during the trial was not adequate to yield a response.

In summary, several studies suggest that diverse hematopoietins can induce thrombopoietic responses in bone marrow failure, that some of these responses are multilineage, and that recovery can be durable in a subset of individuals. Future trials using a paradigm of continuous, prolonged therapy with thrombopoietic growth factors in bone marrow failures states merit pursuit.

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