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Review

Osteogenesis imperfecta: exploring an autoimmune and immunotherapy perspective

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Abstract

Osteogenesis imperfecta (OI), also called brittle bone disease, is a genetic osteodysplasia characterized by a defect in type 1 collagen. Often diagnosed in infancy or early childhood, young patients are affected by frequent fractures. Osteogenesis imperfecta was first named almost 200 yr ago, yet there are still no FDA-approved treatments for OI, and existing treatments target only the skeletal defects of the disease. In this review, we briefly examine current treatments and ongoing clinical trials. Then, by analyzing OI with an osteoimmunological perspective, we have compiled evidence that OI has an autoimmune component. This autoimmune component of OI remains unconsidered, even though an immunology-based therapy has shown promise in treating OI. Acknowledging an autoimmune component of OI is critical to understanding its mechanisms and allowing for the development of more efficacious treatments and novel immunotherapies. Considering the existing literature and the growing impact of immunotherapeutic therapies in cancer and other autoimmune diseases, we believe it may be time to rethink the immune aspects of this genetic disorder and develop novel immunomodulating strategies to improve the quality of life for OI patients.

Keywords: osteogenesis, autoimmunity, immunotherapy, Treg, T cells, cytokines, inflammation

Lay Summary

Patients with brittle bone disease frequently break their bones. Treatments often involve physical repairs such as surgery or repurposed medicines for bone health. In recent times, however, the immune system and bone appear strongly linked. In this paper, we investigate new evidence that brittle bone disease could also have an immune component to its' pathogenesis and how new treatments rooted in immunology could also be beneficial to patients with osteogenesis imperfecta (OI).

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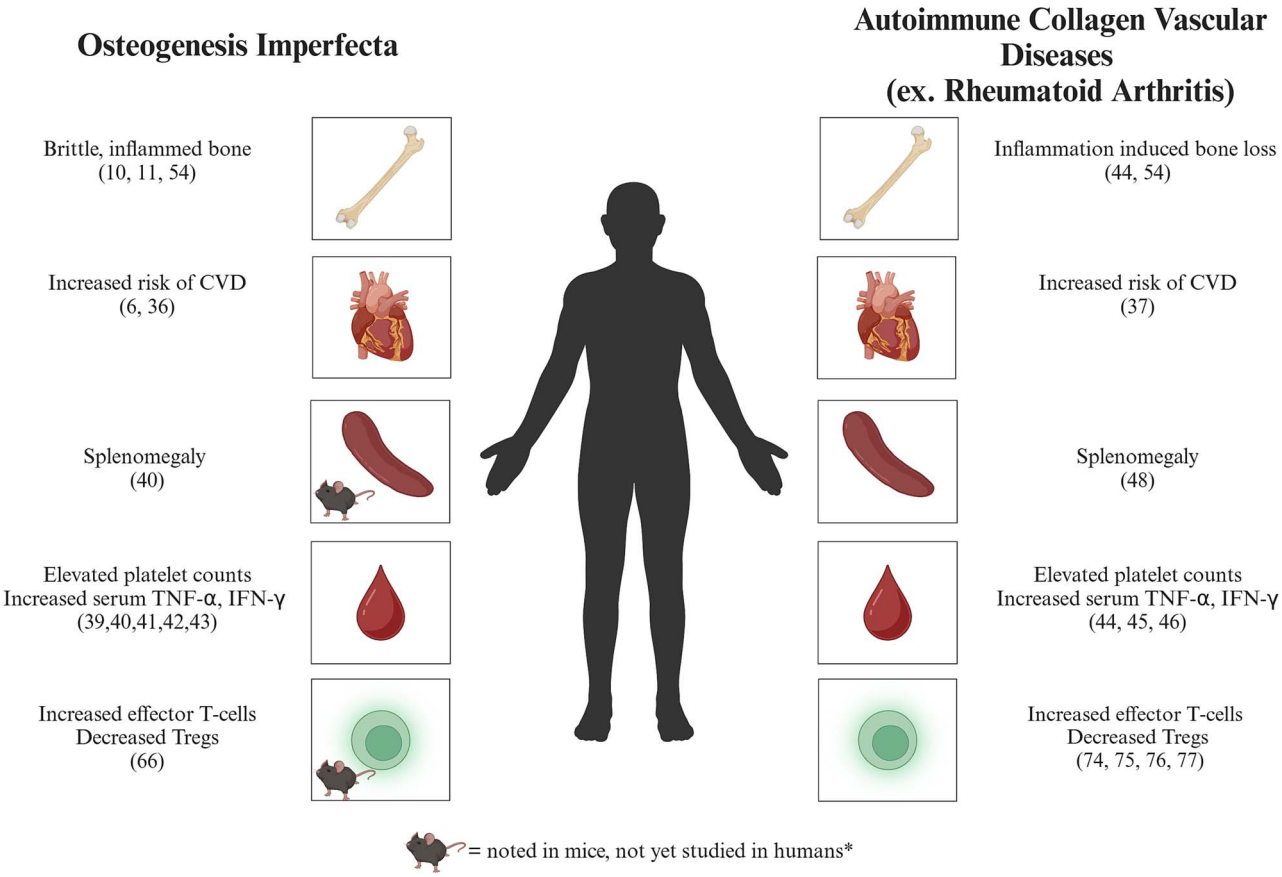
Graphical Abstract



What is osteogenesis imperfecta

Osteogenesis imperfecta (OI), or brittle bone disease, is the most common heritable connective tissue disorder characterized by a defect in type I collagen.[1] OI is by no means a new disease, with the clinical features of OI found in ancient Egyptian mummies. The term osteogenesis imperfecta was coined in the first half of the 19th century, and the genetic link was noticed shortly thereafter.[2] Signs of OI vary depending on its type but often include easy and frequent low energy fractures, bone deformities and short stature. OI can also affect systems beyond bone. Patients with OI have increased incidences of dental abnormalities, such as dentinogenesis imperfecta[3] and malocclusion[4] as well as blue sclera,[5] hearing loss, and cardiovascular and neurological issues.[6,7] OI is genetically highly heterogeneous. Sillence and Danks initially classified OI into four types in 1979.[8] These classical OI types (type I mild, type II perinatal lethal, type III severely deforming, and type IV moderately deforming) are dominantly inherited disorders caused by a quantitative or a structural defect in *COL1A1* or *COL1A2* genes which code for the α1(I) and α2(II) chains of type I collagen, the major protein in the extracellular matrix.[8] OI is currently defined as a collagen-related disorder that can also be caused by defects in proteins involved in collagen folding, post-translational modifications and processing, bone mineralization, and osteoblast differentiation, with its inheritance being autosomal dominant and recessive as well as X-linked recessive.[9,10] The treatment goals for OI have remained focused on only the skeletal defects of the disease and perhaps, have not considered other aspects of its pathogenesis, despite the discovery of new types and mechanisms of the disease. Clinicians treat OI by attempting to increase physical strength or mechanically supporting the bone. Such treatments include physical therapy, rehabilitation, bracing, splinting, etc. In severe cases, OI interventions can also be surgical, including temporary insertion of intramedullary rods or locking plates.[11,12] However, the most widely used treatment for OI are mainly pharmacological and involve using pharmaceuticals in an attempt to increase bone strength and decrease fractures. These pharmaceuticals include bisphosphonates (BPs), antibody-based therapies, and synthetic hormones, to name a few.[13] These first 3 pharmacological interventions will be discussed in greater depth in the following section of this review. Simply put, current non-pharmaceutical treatments are skeletal based. In addition, these physical/mechanical interventions target the skeleton in an attempt to decrease or repair fractures and lessen the severity of symptoms related to OI bone deformities.

Current pharmacological treatments

OI is classified as a genetic osteodysplasia; in fact, it is the most well-known osteodysplasia.[14] Due to this classification, pharmacological interventions for OI target only the skeletal defects of the disease, primarily by repurposing drugs used for osteoporosis. One such treatment, and the one that is most widely used for OI, is a class of drugs known as BPs.[15]

Bisphosphonates were synthesized in the 1800s and were first used clinically to treat bone disorders in 1968.[16] Therefore, they are the most well-studied drugs used to increase BMD. In the case of OI, BPs have been the gold standard treatment for at least 30 yr.[17] BPs work by binding directly and relatively permanently to the bone to inhibit osteoclasts.[18] This osteoclast inhibition prevents the resorption of bone to increase mineral density.[19] However, this prolonged binding also raises concerns over the long-term usage of BPs. When the BPs bind, they do not leave the bone until it has been remodeled. With BPs directly inhibiting this remodeling, they have an extremely long half-life estimated to be around ten years in humans.[20] This long half-life is a concern as long-term suppression of bone turnover can ironically decrease bone quality and lead to increased fractures and bone fragility over time.[21] For instance, long-term, high dosage of BPs is associated with osteonecrosis of the jaw and atypical femoral fractures, both of which are thought to be related to this over-suppression of bone turnover.[22] In addition, BPs are not effective in all patients. A review of 14 OI BP studies established that these studies could not determine a statistically significant decrease in fractures in the BP group over the placebo group.[23] Regardless of the potential consequences of long-term use and limited effectiveness, BPs remain the standard of care for OI.

An alternative to the BPs is denosumab. Denosumab is a monoclonal antibody that inhibits the interaction between the RANKL and its receptor RANK, thereby inhibiting osteoclast formation, but without the long-term binding to bone that occurs with BPs. Thus, denosumab's half-life is significantly shorter than BPs.[24,25] The shorter half-life of denosumab addressed one of the previously mentioned concerns about BP use. However, somewhat ironically, due to denosumab's much more temporary action, the positive effects of denosumab are rapidly reversed after treatment is stopped.[26] This rapid reversal of effects resulted in denosumab being associated with potentially dangerous rebound hypercalcemia in children.[27] This rebound hypercalcemia is thought to be related to rapid bone resorption that occurs after denosumab usage is stopped.[26,27]

Another promising, bone-targeting, neutralizing antibody currently undergoing clinical trials in pediatric patients with OI is an anti-sclerostin antibody known as Setrusumab. In the phase 1 and 2 trials, a fracture reduction and increase in BMD was seen.[17] However, as with any drug in its preliminary stages of trials, there are questions about whether this effect will persist when the treatment is stopped. This concern stems from drugs like denosumab, which worked well in the early stages; only when the drug use was stopped did the rebound hypercalcemia reveal itself.[24,25] Another concern with setrusumab is whether the therapy can be continued long-term. The concern of long-term use is related to the side effects of a similar antibody therapy—specifically, romosozumab, another anti-sclerostin antibody drug used for the treatment of osteoporosis. Romosozumab showed an increase in severe cardiovascular adverse events with long-term use.[28] Some believe this side effect could be related to sclerostin's impact on the calcification of vasculature,[29,30] although any potential mechanism is not defined.[30]

Another medication sometimes used to treat OI is synthetic parathyroid hormone (PTH) teriparatide. Teriparatide can increase bone density in adults but cannot be used in children due to an increased risk of osteosarcoma.[31] Teriparatide has also been associated with increased calciphylaxis in adults,[32] a consequence of high PTH levels in the blood.[33]

Thus, current pharmacological treatments for OI have varying levels of success and many potential side effects. It should be noted that in addition to BPs, denosumab, and teriparatide, other treatments are being developed (like setrusumab). However, the efficacy of presently accepted or newly developing bone-related treatments will not be the focus of this review as there are many existing and excellent reviews on current OI treatments. Though one such review states the disadvantage of the current OI treatments are "their relatively weak effectiveness, lack of effects in some patients or cytotoxic side effects."[15] This led us to reexamine the disease from a fresh, immunological perspective for our studies and in this review, something which has not been comprehensively studied previously. We hope such a perspective could one day lead to more efficacious treatments.

More than bone

As stated in the previous sections, current treatments for OI have only targeted skeletal defects. However, the disease can affect systems beyond the skeleton. For example, OI has been associated with adverse cardiovascular effects. A nationwide longitudinal cohort study conducted in Denmark found those with OI to be at a significantly increased risk for cardiovascular disease.[6] OI's effect on the cardiovascular system is not surprising, as healthy type I collagen is essential in heart valves, chordae tendineae, fibrous rings, interventricular septum, aorta, and other arteries.[34,35] However, this leads to the question of whether, in addition to being a skeletal dysplasia, OI could also be a collagen vascular disease.

Collagen vascular diseases are a group of autoimmune conditions that cause chronic systemic inflammation. Furthermore, in these diseases, cardiovascular events are the primary cause of death.[36] Ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), rheumatoid arthritis, and scleroderma are some of these collagen-vascular diseases.[37] It is well known that OI affects type I collagen, and emerging evidence suggests OI is associated with cardiovascular issues. However, to be potentially grouped with other collagen vascular diseases, systemic inflammation and autoimmunity criteria would also need to be clearly identified and defined.

Interestingly, recent evidence has emerged to support the idea that OI can have an autoimmune component. New studies have shown a potential activation of inflammatory pathways in OI.[38] For instance, splenomegaly and increased serum TNF-α levels were identified in a model of OI mice (B6C3Fe a/a-*Col1a2*^{oim}*/J*).[39] Such features are indicative of low-level systemic inflammation.[39] Additionally, RNA sequencing showed upregulated IL-17 and TNF-α signaling in bone marrow cells from young male OI mice (heterozygous B6C3Fe a/a-*Col1a2*^{oim}*/J* and *Col1a1*$^{+/-365}$, a *Col1a1* gene knock-down that can simulate OI type I).[40] Furthermore, the inflammatory component in OI extends beyond the mouse models. It has been noted that pediatric OI patients present a hyper inflamed condition with increased platelet counts, even in the absence of any recent fractures.[41] In addition, peripheral blood transcriptome analysis demonstrated an upregulation of IFN-γ and TNF-α signaling pathways in OI patients.[42] It is important to note that TNF-α is a critical inflammatory cytokine in rheumatoid arthritis (RA),

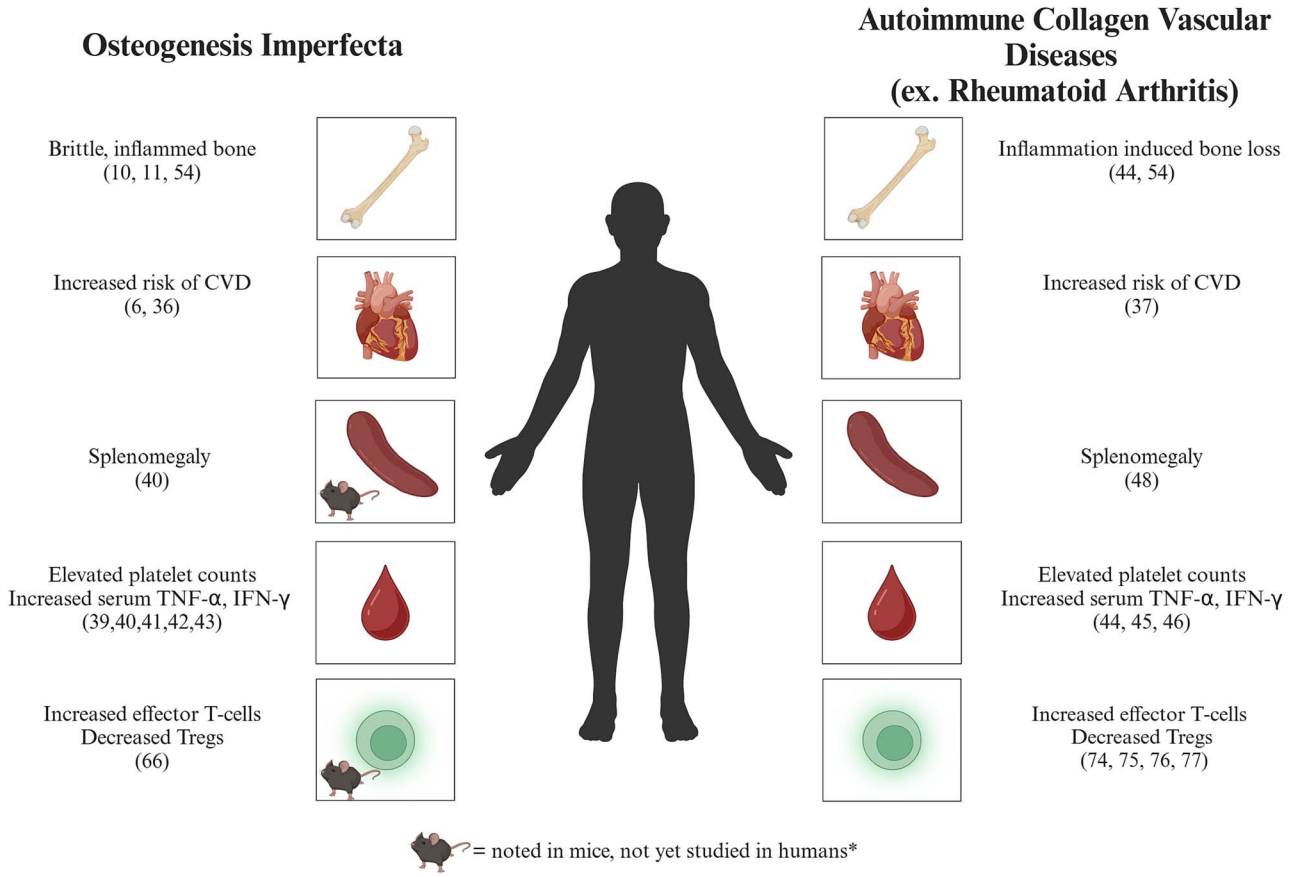


Figure 1. Similarities between OI and rheumatoid arthritis (a collagen vascular disease). *Created with Biorender.com.*

a collagen vascular disease. In RA, TNF-α is believed to be the major driver of collagen breakdown associated with the disease.[43,44] Monocytes in the B6C3Fe a/a-*Col1a2*^{oim}/*J* OI mouse model highly express TNF-α and synthesize RANKL,[39] a crucial factor of bone erosions in RA.[45,46] Another similarity between RA and OI is that splenomegaly has been noted in human patients with RA,[47] much like in the B6C3Fe a/a-*Col1a2*^{oim}/*J* OI mice.[40] Thus, studies have pointed out a link between RA and OI,[48,49] which will require further investigation. Similarities between OI and RA can be visualized in Figure 1. Nonetheless, it points toward the fact that inflammation may play an essential role in OI, though confirmatory studies in other OI mouse models as well as human OI patients is needed to confirm these exciting but sparce observations that exist in literature.

The relationship between bone health and immunity has become more apparent in recent years. The relatively new field of osteoimmunology has increased the understanding that immune cells and bone cells are highly linked in their processes.[50] Previous studies have shown that inflammation can lead to excessive bone resorption due to upregulation or hyperactivity of osteoclasts, as well as impaired bone formation due to downregulation or hypoactivity of osteoblasts.[51–53] Thus, prolonged inflammation increases bone resorption and decreases bone formation, thereby decreasing bone quality.[54] Additionally, thanks to osteoimmunology studies, it has recently been discovered that this effect is not unidirectional, and that bone can also affect immune regulation. Specifically, both osteoblasts and osteoclasts have been found to affect T-cell and B-cell differentiation directly, contribute to hematopoietic malignancies, and influence immune cells in systemic disease.[55] Another potential explanation of why OI may have a systemic inflammatory component is that defective collagen may trigger this inflammatory response.[56] Therefore, considering the great degree of interconnectedness between the skeletal and immune systems, it seems worthwhile to investigate OI's inflammatory, immunological component further with confirmatory studies in additional OI mouse models and in human OI patients, to add to the sparse observations that exist at this time in literature.

Immune cells and pathways in OI

In its first phase of human clinical trials, a newly developed treatment for OI attempts a less skeletal-based and more immunological approach by targeting TGF-beta (TGF-β). TGF-β is a complex pleiotropic secreted protein with both immunosuppressive and stimulatory functions, depending on cell type.[57] The basis of this clinical trial was a study that found TGF-β target genes to be highly expressed in OI bone in dominant and recessive murine models (*Crtap*$^{-/-}$ and *Colla2*$^{tm1.1Mcbr}$) than in WT mice.[58] This TGF-β-mediated pathogenesis was speculated to be related to the inability of mutated type I collagen to bind to the small leucine-rich proteoglycan decorin, which is a known regulator of TGF-β activity.[58,59] In addition, when this group neutralized TGF-β with an antibody, bone parameters in these mice strains were positively affected. They also showed excessive TGF-β

signaling in human OI bone and conducted a phase I clinical trial focused on neutralizing TGF-β with fresolimumab, an FDA-approved anti-TGF-β antibody.[60] The effect on LS aBMD was inconsistent in this trial. Out of the 8 enrolled patients, there was a variable increase in the LS aBMD in OI type IV patients, but LS aBMD decreased or did not change in other OI patients.[60] TGF-β has highly complex signaling, and in addition to its effects on bone, it can also have anti-inflammatory and immunosuppressive effects.[61] But can also cause pro-inflammatory and autoimmune responses, with these effects being highly context-dependent.[62,63] Nonetheless, the understanding of the critical importance of TGF-β in regulating the immune response[64] combined with the discovery of abnormal TGF-β signaling in OI bone, seems to further elucidate an immunological component of OI.

Even though systemic inflammation has been recently reported in OI, there was no study to comprehensively examine the immune profile in OI mice, specifically the T cell populations. In our 2022 study, we analyzed the T cell subsets in OI mice. We demonstrated that OI mice (B6C3Fe a/a-*Col1a2^{oim}/J*[65] do exhibit an activated T cell phenotype with an increased ability to secrete the inflammatory cytokines, IFN-γ and TNF-α.[65] We do accept that the data in our study was generated using the B6C3Fe a/a-*Col1a2^{oim}/J* mouse model of OI. Though this is a widely used and well accepted model of OI, the collagen mutation in it results in absent Col1a2 chain of type I collagen, thereby the collagen molecule is a homotrimer of Col1a1. This is a rare and unusual form of type I collagen and one that could trigger autoimmune/inflammatory reactions. Hence, there is a need to study additional mouse models of OI to confirm our findings. Therefore, since our published study, we have also confirmed this phenotype in *Col1a2$^{(+/G610C)}$* model of OI (unpublished results). Therefore, a pro-inflammatory environment exists in some murine models of OI with increased levels of inflammatory cytokines in the circulation. We also acknowledge the need for studies of additional OI mouse models to confirm the breadth of these findings. These chronic elevated systemic levels of pro-inflammatory cytokines can induce the proliferation of osteoclast precursors, which can differentiate into mature osteoclasts to cause further bone destruction.[66] It has been demonstrated that even though there exists a state of high bone turnover in OI, the high rate of bone formation cannot compensate for the much higher rate of bone resorption due to the increased formation and activity of osteoclasts.[67,68] Thus, it is plausible that the hyperactivity of the osteoclasts seen in OI may be exaggerated due to the increased levels of inflammatory cytokines released from immune cells. Recent reports have also shown that pro-inflammatory cytokines, especially TNF-α, can inhibit osteoblastogenesis and bone formation.[69–72] Our unpublished data shows that calcium deposition by osteoblasts (measured by Alizarin red staining) was significantly reduced when cultured in the conditioned media from activated T cells. Therefore, the activated T cells and the pro-inflammatory environment present in OI can affect bone resorption and bone formation by influencing the formation and activity of osteoclasts and osteoblasts.

In addition to the systemic inflammation seen in OI, our study also identified the probable cause of these pro-inflammatory conditions. OI mice (B6C3Fe a/a-*Col1a2^{oim}/J*) were discovered to have consistently and significantly lower numbers of T-regulatory cells (Tregs).[65] Furthermore, this decrease in Treg numbers has been confirmed in *Col1a2$^{(+/G610C)}$* (unpublished results). Treg cells are a subset of T lymphocytes, essential in suppressing the immune response and providing self-tolerance.[73] The decreased number of Tregs is another similarity between OI and RA, as patients with RA have also been found to have a reduced proportion of Tregs compared to healthy individuals.[74] Decreased Tregs are also being investigated as a potential contributor to SLE[75] and AS,[76] both of which are classified as autoimmune collagen diseases. With this recent discovery of decreased Tregs and systemic inflammation in some mouse models of OI, it is time to consider the autoimmune aspects of OI in addition to considering it to be a skeletal dysplasia. A timeline of this emerging evidence can be seen in Table 1.

Possible causes for decreased Tregs in OI

It is not entirely clear why the number of Tregs is decreased in a genetic disease that has mutated or reduced collagen. However, clues can be taken from the studies which show that treating naïve T cells with collagen-derived peptides promoted the development and differentiation of Tregs in vitro[77] and feeding mice polymerized-type I collagen upregulated Treg differentiation in vivo in mouse models of early and established arthritis.[78] Furthermore, it has been shown that collagen concentration and alignment can increase the percentage and infiltration of Tregs in breast cancer models.[79] OI can have decreased amounts of collagen (seen in type I OI) and an altered molecular structure that exerts a dominant-negative effect on collagen fibril formation and function.[80] Thus, the collagen deficiency and mutation seen in OI may affect the Treg generation, but further studies are needed to confirm this.

Several cytokines are essential for the development of Tregs, the most important being TGF-β and IL-2.[81] As mentioned above, it has been shown that excessive TGF-β signaling is a common mechanism in OI.[58] We also confirmed the presence of elevated levels of TGF-β in the serum of OI mice (B6C3Fe a/a-*Col1a2^{oim}/J*; unpublished data). However, our data also shows that TGF-β receptor I and II expression was significantly reduced in splenic T cells from OI (B6C3Fe a/a-*Col1a2^{oim}/J*) mice compared to WT mice.[65] Therefore, despite the elevated levels of TGF-β in OI, TGF- β signaling in T cells is likely dampened, leading to reduced generation and maintenance of Tregs. So, the question of what factor (s) might be responsible for the reduced Treg numbers in OI is the subject of ongoing and future studies in our lab.

Decreased Tregs, osteoblasts and osteoclasts

Tregs can directly affect the osteoclasts and osteoblasts. Their effects on osteoclasts are well documented. Studies have shown that Tregs can regulate the number of osteoclast precursors as well as affect osteoclast development and function either via cell-to-cell contact or by the release of cytokines such as TGF-β, IL-4, and IL-10.[82–85] Our data shows that conditioned media from Tregs, both from WT and OI mice (B6C3Fe a/a-*Col1a2^{oim}/J*),[65] significantly reduced osteoclasts' formation in vitro in OI bone marrow cell cultures, indicating Tregs' effects in OI seem to be mediated by cytokines.[65] However, the nature and the role of the cytokines involved, the stage of osteoclastogenesis where the inhibition occurs, and the mechanism of the inhibition

Table 1. Timeline of new evidence that has emerged to support the idea OI has an inflammatory/immune component.

Emerging evidence of inflammatory/immune component of osteogenesis imperfecta			
Feature	**Year**	**Study type**	**Findings**
Elevated TGF-B signaling[58]	2014	*Crtap*$^{-/-}$ and *Colla2*$^{tm1.1Mcbr}$ mouse bone	Excessive TGF-B signaling observed, neutralizing TGF-B restored bone phenotype
Increased risk of CVD[6]	2016	Population and register-based longitudinal open cohort study of OI patients	Patients with OI are at an increased risk of CVD compared to the general population This included increased risk of heart failure, increased risk of atrial fibrillation, increased risk of aortic and mitral valvopathies
Phenotype suggestive of chronic inflammation[39]	2017	Osteogenesis imperfecta murine (B6C3Fe a/a-*Col1a2*^{oim}/*J*) mouse model	Splenomegaly in all OI mice Increased TNF-a levels in all mice Expansion of myeloid lineage (CD11b+) cells
Increased pro-inflammatory reaction[38]	2018	Crispr -Cas9 genetic knock-in of OI type V mouse model	OI type V knock-in mice had upregulated Ptgs2 and Nr4a3 compared to WT, suggesting activation of a pro-inflammatory reaction
Elevated platelet counts in OI patients[41]	2018	Retrospective cohort analysis of children with moderate to severe OI	Elevated platelet counts indicative of systemic inflammation were observed in children with OI, even in the absence of identified pro-inflammatory factors such as recent fractures
Elevated inflammatory signaling in OI patients[42]	2020	Transcriptomic analysis of whole blood of OI patients	Found pro-inflammatory signaling changes in IFN, MAPK, Ras, Notch, TNF and WNT signaling pathways
Increased inflammatory signaling[40]	2022	Male *Col1a1*$^{+/-365}$ and heterozygous B6C3Fe a/a-*Col1a2*^{oim}/*J* mice RNA-seq of bone marrow cells	Dysregulated response to interferon (IFN) Upregulated IL-17 Upregulated TNF signaling
Systemic inflammation and immune phenotype[65]	2022	B6C3Fe a/a-*Col1a2*^{oim}/*J* mouse model	Increase in pro-inflammatory cytokines in circulation (TNF-a, IFN-y) Decrease in Treg numbers Increase in activated effector T-cells

in OI are the focus of future studies in our lab. In contrast to osteoclasts, the effects of Tregs on osteoblasts or their progenitors are under investigation. A study has demonstrated a positive effect on bone healing upon administration of combined Treg and bone marrow mesenchymal stromal cells (MSCs) in a calvarial defect model in mice. However, the underlying mechanisms have not been revealed.[86] A couple of studies have shown that PTH exerts its bone anabolic activity by increasing the number of Tregs, as the blockade of Tregs hamper bone formation and trabecular bone volume and structure induced by PTH.[87] The same group further shows that Tregs increase the production of Wnt10b from the $CD8^+$ T cells, which can stimulate bone formation by activating Wnt signaling in osteoblasts.[88] Thus, Tregs have been implicated in playing a role in bone formation by promoting the proliferation and differentiation of osteoblasts directly or by secreting cytokines and activating downstream effectors that induce mesenchymal stem cells to differentiate into osteoblasts.[89–91] Our data demonstrate that conditioned media from both WT and OI (B6C3Fe a/a-*Col1a2*^{oim}/*J*) Tregs augments the differentiation of cultured osteoblasts from OI mice as it significantly increases calcium deposition.[65] The factors secreted by Tregs that play a role, and the mechanisms involved in OI's osteoblastic differentiation will be the subject of future studies.

Potential immunologic treatment for OI: adoptive Treg transplant

As discussed, treatment options for OI remain quite limited, with new treatments being investigated daily. Although additional confirmatory studies are required to further support our immunological observations, if an autoimmune component of OI is present, like in collagen vascular diseases such as RA, an entirely new world of treatments that can be developed will arise. One potential immune-related treatment we highlighted in our study is adoptive Treg transplantation.[65]

Adoptive Treg transplantation, like other adoptive T-cell therapies, involves isolating T lymphocytes from the peripheral blood, generating Tregs, expanding them, and then transfusing them into the patient.[92] Our study shows that such Treg therapy can effectively alleviate some of the pathologies of OI in the B6C3Fe a/a-*Col1a2*^{oim}/*J* mouse model.[65] Systemic transplantation of Tregs into OI mice significantly improved bone architecture, morphometry, and mechanical properties post-transplantation in these affected mice. We also demonstrate that Treg transplantation resulted in decreased T cell activation and a decrease in the effector cytokines IFN-γ and TNF-α. Furthermore, it has been shown that the adoptive transfer of Tregs into T cell-deficient RAG-1 knockout mice increased bone mass in these mice, indicating that Tregs probably can directly affect bone homeostasis without the need to engage other T cell lineages.[93] This increase in bone mass was due to a decrease in bone resorption while bone formation remained unchanged. In contrast, morphometric analyses in our study demonstrate that in addition to decreased osteoclast numbers and function, adoptive Treg transplantation in OI mice also resulted in a significant increase in the number of osteoblasts and their differentiation.[65] This finding indicates that Treg transplantation can be beneficial in treating OI by dampening the pro-inflammatory environment and increasing bone health, though further confirmatory studies are needed in different OI mice models.

Treg transplantation is gaining widespread attention as Tregs offer a new therapeutic option for controlling undesired systemic and local immune responses.[94] Treg transplantation is already being used as a therapy for various diseases, including Type 1 diabetes (T1D), and in the prevention of graft versus host disease (GvHD) in those with solid organ transplantation.[95–100] Furthermore, there is evidence supporting the idea that Tregs have a positive effect on bone growth in cases other than OI. For instance, transgenic mice overexpressing FoxP3, the main transcription factor of Tregs, have higher bone mass than their wild-type counterparts. As previously mentioned, a study also found that transferring Tregs into T cell-deficient RAG-$1^{(-/-)}$ mice increased bone mass in these mice.[93] Another study found systemic infusion of $FoxP3^{+}$ Tregs significantly improved bone marrow mesenchymal stem cell-based bone regeneration and calvarial defect repair in C57BL/6 mice by reducing the levels of IFN-γ and TNF-α.[86] Furthermore, systemic infusion of bone marrow MSCs significantly enhanced the repair of critical-sized calvarial defects in C57BL/6 mice via Tregs' upregulation.[101] In a canine model of periodontitis, it has been shown that Tregs are recruited to the site of the injury and decrease bone resorption by reducing inflammation.[102] It has been demonstrated that the adoptive transfer of Tregs can bring about enhanced bone healing in an osteotomy model.[103] There is even evidence relating Treg therapy to the current, most widely used treatment for OI, the BPs. It was discovered that BPs may cause an elevation in the levels of cytokines IL-10 and TGF-β, which are the most heavily secreted cytokines by activated Treg cells[104] and have been shown to expand and differentiate Tregs in the blood of osteoporotic patients.[105] This evidence suggests that BPs may exert some of their effects via Tregs rather than acting directly on bone alone. We believe that the effects of Tregs in OI are 2-fold; Treg transplantation helps dampen the pro-inflammatory environment seen in OI, which positively impacts bone. Additionally, Tregs may also act directly on the bone cells to decrease the activity of osteoclasts and increase the activity of osteoblasts to increase bone remodeling positively. Additional studies are needed to examine the factor(s) from the Tregs that bring about this action and whether cell-to-cell contact is also essential for this function.

Although Treg transplantation therapy is in its infancy, it has shown promise in human patients with autoimmune diseases. Tregs have also been shown to be effective in improving bone conditions such as calvarial defect and periodontitis, and recently, in a mouse model of OI. We believe that, eventually, Treg transplantation could be a more effective treatment for OI in humans. However, for Treg transplantation to be seriously considered as a potential therapy for OI, it is essential that OI is viewed in an autoimmune context. Additional confirmatory immunological studies confirming the presence of an autoimmune component of OI would allow immunosuppressive treatments, like Treg transplantation, to be viewed as logical and potentially feasible therapies for this disease.

Conclusion

New evidence indicates that there is an immunological/inflammatory component in OI. This disease has historically been treated for the skeletal defects related to a mutation in type I collagen. If these recent discoveries of the presence of systemic inflammation and increased risk of cardiovascular disease are confirmed in various mouse models and in patients, OI will appear to be closely related to autoimmune collagen vascular diseases. These observations, combined with the noted decrease in Tregs in some OI mouse models and the restorative effect on bone of Treg transplantation, warrants a new perspective when seeking potential novel treatments for OI. Perhaps the immune system plays a particularly important role in the pathogenesis of OI, or maybe its role intertwined with the traditional skeletal pathology. These can be the subjects of additional studies in the future. Although Treg transplantations are in their infancy in human clinical trials for treating other autoimmune disease, they could hold promise as an eventual treatment for OI. However, adoptive Treg transplantation will likely not be considered as a viable treatment option until the autoimmune component of OI is further verified and studied. Therefore, it is vital to view and further investigate OI with an immunological lens to better understand the mechanisms contributing to the disease. Hopefully, this newfound knowledge will allow for the creation and implementation of more effective treatments.

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J.G. contributed to the drafting and editing of the review. M.M. and S.M. contributed to the conceptualization and editing of the review. Figure was prepared by J.G. using Biorender.com.

Author contributions

Jackson F. Goddard (Conceptualization, Investigation, Writing—original draft), Shikhar Mehrotra (Conceptualization, Writing—review & editing), and Meenal Mehrotra (Conceptualization, Writing—review & editing)

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Conflicts of interest

The authors have no conflict of interest.

Data availability

All sources cited in this review article can be found online. The unpublished data mentioned in this article will be shared by the corresponding author on request.

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