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Anti-thymocyte globulins in kidney transplantation: focus on current indications and long-term immunological side effects

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ABSTRACT

Antithymocyte globulins (ATGs) are part of the immunosuppression arsenal currently used by clinicians to prevent or treat acute rejection in solid organ transplantation. ATG is a mixture of non-specific anti-lymphocyte immunoglobulins targeting not only T cell subsets but also several other immune and non-immune cells, rendering its precise immunoglobulin composition difficult to appreciate or to compare from one preparation to another. Furthermore, several mechanisms of action have been described. Taken together, this probably explains the efficacy and the side effects associated with this drug. Recent data suggest a long-term negative impact on allograft and patient outcomes, pointing out the need to better characterize the potential toxicity and the benefit–risk balance associated to this immunosuppressive therapy within large clinical trials.

Keywords: ATG, immune cell reconstitution, kidney allograft survival, serum sickness disease, transplant outcomes

INTRODUCTION

Due to its capacity to deplete T and B cells, to inhibit B and T cell cooperation as well as leucocyte adhesion and to induce certain 'tolerogenic' regulatory T cell and dendritic cell (DC) populations, antithymocyte globulin (ATG) is a good candidate drug to prevent and treat both acute T cell (TCMR) and antibody-mediated rejection (ABMR). Despite limited evidence from randomized clinical trials, ATGs have been widely used as an induction therapy in renal transplantation for high-risk immunological patients for many decades. ATG has also been used as a first-line therapy for TCMR, in particular, those with severe acute TCMR including vascular lesions (≥Banff II categories) and as rescue therapy for steroid-resistant acute TCMR. Nevertheless, its superiority to other therapies (e.g. steroid bolus, intense tacrolimus therapy) in those indications remains a matter of debate. Again, there is a lack of adequately powered clinical trials with contemporary immunosuppression. While efficacy is not disputed, the numerous short- and long-term side effects make a risk–benefit assessment versus other less toxic therapies difficult, and unfortunately some of the side effects are associated with inferior long-term outcomes with regard to patient and graft survival. Indeed, ATG results in a profound depletion and modification of the recipient's immune system, which probably explains the higher risk of opportunistic infections and cancer. A recent published study from Couvrat-Desvergnes *et al.* [1] about the negative impact of ATG-induced serum sickness disease (SSD) on allograft survival has reopened the debate on the intrinsic toxicity of this powerful immunosuppressant in kidney transplantation. In this review we aim to summarize the current knowledge on the mechanism of action, discuss the evidence-based literature justifying the different therapeutic indications of the drug and, finally, discuss recent data analysing the possible pathogenic processes supposed to be involved in the long-term negative impact of ATG on renal transplant recipients' outcomes.

MECHANISM OF ACTION OF ATG

ATG is polyclonal immunoglobulin G (IgG) fractions purified from sera of rabbits or horses previously immunized with human lymphocytes. The sources of lymphocytes are human spleen, blood, thymus or lymphoblastic lineages. After purification, polyclonal cytotoxic antibodies are isolated and able to target numerous immune cell clusters of differentiation and membranous antigens (e.g. CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA type I etc.) [2]. After infusion, ATG induces immediate immune cell depletion, particularly T lymphocyte depletion, through four currently known mechanisms [3–5]:

(i) The antibody-dependent cell cytotoxicity pathway is the main mechanism and is the consequence of fixation of the polyclonal antibodies on its specific antigens, while the Fc part of the antibodies are recruiting Fcγ receptor cytotoxic cells [macrophages and natural killer (NK) cells].

(ii) The complement-dependent cell cytotoxicity is dose dependent and related only to those antibodies that are able to fix complement C1q with their Fc part. These complement fixing antibodies will initiate the formation of the membrane attack complex (MAC) mC5b-9, causing the lysis of the targeted cells.

(iii) The opsonization process involves phagocytosis of antibody-recovered T lymphocytes by the reticulo-endothelial network.

(iv) The activation-induced cell death pathway occurs through the antibody-induced and cytokine-mediated upregulation of CD178 (CD95-L) expression by resting T cells. The Fas-Fas ligand pathway activation induces T lymphocytes apoptosis.

In addition to T-cell depletion, ATG may also result in less T cell activation by the downregulation of molecules that control T cell activation, such as the TCR/CD3 complex, CD2, CD4, CD5, CD6 and CD8. [2]. ATG infusion may cause a cytokine release syndrome, which may activate numerous inflammatory cells and is responsible for the acute side effects during rapid infusion. Finally, ATG could act on leucocyte adhesion through downregulation of the cell surface expression of several integrins and intercellular adhesion molecules (e.g. ICAM-1, VCAM, PECAM, CD11b and CD62e) [6]. This effect inhibits leucocyte adhesion to the endothelium, as shown *in vivo* by Chappell *et al.* [7] in an ischemia-reperfusion non-human primate model.

ATG and immune reconstitution

T cell reconstitution. Peripheral T cell depletion after ATG is almost complete (98%) and concerns more naïve than other T cell populations, i.e. memory and Treg cells [8]. Preville *et al.* [2] showed in a non-human primate model that ATG-induced T cell depletion predominantly affected peripheral blood T cells and peripheral lymphoid tissues, but not the thymus. Ruzek *et al.* [8] studied the effects of anti-murine rabbit ATG (mATG) administered to C57BL/6 mice. Although mATG depleted thymocytes *in vitro*, there was no thymocyte depletion *in vivo* at any dose level, suggesting decreased antibody accessibility in the thymus. Nevertheless, the effects of ATG on human thymic function have never been assessed and the thymic output in adults has been demonstrated to play a role in immune reconstitution, particularly during lymphopenia in the context of bone marrow transplantation [9] and HIV [10, 11]. About 40% of patients treated with thymoglobulin (mean of 6 doses at 1.5 mg/kg/day) recover >50% of initial lymphocyte count at 3 months [12]. Yet, time to immune reconstitution is characterized by not only a high intra-individual variability according to the immune cell subpopulations (T and B cells, NK cells, DCs), but also an interindividual variability leading to prolonged lymphopenia for some patients up to 5 years [13, 14]. Some data suggest that despite the absence of thymus accessibility, thymic residual output prior to ATG administration could predict individual lymphocyte reconstitution [15]. In summary, ATG infusion may cause long-lasting effects on lymphocyte populations and the immune system.

Reconstitution of other immune cells. Thus the effect of ATG on T cells is well described, but it is less studied for other immune cells. ATG induces *in vitro* apoptosis of naive activated B cells and bone marrow resident plasma cells, involving the caspase- and cathepsin-mediated apoptosis pathways after the binding of different cross-linking molecules like CD30, CD38, CD95, CD80, CD138 and HLA-DR [16, 17].

ATG could act through different pathways to control B cell activation and antibody formation, which is an interesting aspect for acute humoral rejection:

(i) interference with T cell–dependent activation of alloreactive B cells by removing $CD4^+$ T helper lymphocytes,

(ii) binding to cell surface proteins shared by B and T cells and/or thymocytes with subsequent complement-mediated B cell lysis, and

(iii) binding to unique B cell surface markers that interfere with B cell activation and induce apoptosis.

The latter pathway could be possible, as human paediatric thymi are used to immunize rabbits and have been shown to contain 2–6% of B, plasma and dendritic cells [18, 19]. Yet, *in vivo*, no depletion of bone marrow and spleen plasma cells has been demonstrated [17, 20], questioning the clinical relevance of the B cell effects observed *in vitro*.

NK cells are rapidly depleted after ATG infusion with a better reconstitution of the NK population expressing inhibitor receptors with preservation of their secreting (interferon-γ) and cytotoxic functions [21]. Myeloid and plasmacytoid DCs are eliminated up to 80–85% with an *in vitro* maturation polarization to a tolerogenic profile [22]. More data are needed to better understand the effects of ATG on these important immunomodulatory cell types and their clinical consequences.

THERAPEUTIC INDICATIONS FOR ATG

ATG as prophylactic induction therapy in solid organ transplantation

Prophylactic immunosuppression in many countries, particularly the USA, has featured the emergence of 'induction' treatments using biological polyclonal depleting agents (ATGs) [23, 24]. Induction therapy with these powerful agents results in initially lower graft rejection rates [25–34], allowing early steroid withdrawal [35] and hospital discharge. Eventually, 'mild' rejections, which are easy to treat, and steroid-resistant rejections in highly immunized patients are prevented, while rejections with inferior outcomes such as humoral rejections are less well prevented, suggesting that the benefit of these potent immunosuppressive agents is counterbalanced by other factors. In contrast, it is well documented that induction therapies with T cell–depleting agents carry an increased risk of postoperative opportunistic infections and cancer, especially post-transplant lymphoproliferative disease [30, 36–38]. Importantly, because of fear of these side effects, ATG doses have been reduced over time, necessitating a re-evaluation of risks with current dosing schemes and tacrolimus/mycophenolate maintenance immunosuppression [34, 35].

Based on clinical studies, current 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of potent T cell–depleting antibodies only for patients with high immunological risk [29, 39]. Long-term outcomes of ATG have been analysed with comparison to interleukin-2 receptor (IL-2R) antibodies. A 2010 Cochrane meta-analysis showed better 1-year allograft survival with IL-2Ra induction versus no induction, but when IL-2Ra was compared to ATG (16 studies, 2211 participants), there was no difference in graft loss but there was a benefit for ATG in biopsy-proven acute rejection at 1 year {eight studies: relative risk [RR] 1.30; [confidence interval (CI) 1.01–1.67]}. However this was at the cost of a 75% increase in malignancy [7 studies: RR 0.25 (95% CI 0.07–0.87)] and a 32% increase in cytomegalovirus (CMV) disease [13 studies: RR 0.68 (95% CI 0.50–0.93)]. Interestingly, serum creatinine was significantly lower for IL-2Ra-treated patients at 6 months [four studies: MD −11.20 µmol/L (95% CI −19.94 to −2.09)]. ATG patients experienced significantly more fever, cytokine release syndrome, leucopenia and other adverse reactions associated with ATG administration. The results were independent of the calcineurin inhibitor (CNI), the antimetabolite and the baseline immunological risk of the study population. There was no evidence that effects differed between equine and rabbit ATG [40]. The authors concluded that compared with IL-2Ra treatment, ATG may prevent acute rejection, but compared with IL-2Ra 1/16 patients will develop an additional CMV infection and 1/58 patients will develop an additional malignancy. While the meta-analysis focused on 1-year outcomes, other recent papers reported long-term outcomes [27]. Hellemans *et al.* [41] reveals the benefit of ATG only for 5-year biopsy-proven acute rejection in high immunological risk patients [41], whereas no benefit with regards to acute rejection or allograft survival was demonstrated in low-risk patients [42]. In another long-term follow-up, overall similar long-term results were reported versus basiliximab, despite better rejection prophylaxis for ATG. Until now there has been no firm evidence of better long-term graft survival in patients receiving polyclonal ATG induction therapy versus those who have not. This emphasizes the KDIGO recommendations, for the use of ATG only in high immunological risk patients [39]. In contrast, there is no good evidence supporting the use of T cell–depleting induction for effective rejection prophylaxis during delayed introduction of CNIs in order to have better recovery of the graft from ischaemic injury [43]. Finally, the use of potent T cell–depleting induction is used in many US centres for early steroid withdrawal [25, 44] or complete steroid avoidance. Long-term data on the benefit of such strategies compared with today's recommended standard therapy are sparse [45]. Yet, until now, no other induction therapy has demonstrated the short-term safety of steroid avoidance or early withdrawal in preventing acute rejection [25, 46].

Treatment of acute TCMR

A meta-analysis published in 2006 has evaluated randomized trial data of 14 trials (965 patients) studying monoclonal and polyclonal antibody therapy—including ATG—for treating acute rejection in kidney transplant recipients [47]. Altogether, monoclonal and polyclonal antibody therapy were better than steroids in reversing ongoing rejection [RR 0.57 (CI 0.38–0.87)] and preventing graft loss whether death-censored or including death with a functioning graft [death-censored RR 0.74 (CI 0.58–0.95)]. There was no difference in preventing subsequent rejection [RR 0.67 (CI 0.43–1.04)] or death [RR 1.16 (CI 0.57–2.33)] at 1 year. Focusing on side effects, there were more fever, chills and malaise following antibody administration, directly related to its mechanism of action. Unfortunately, all these clinical trials did not systematically report side effects and a definitive conclusion on infectious and long-term neoplastic consequences could not be drawn from these studies. Overall reporting quality was poor and incomplete, rejections were not defined according to current standards (no biopsies required, all trials before the first Banff classification) and baseline immunosuppression outdated (no trial with tacrolimus or mycophenolate), as all trials were published before 1998. The authors concluded that the review is limited by the quantity and quality of published trials, and even the meta-analysis could not answer the underlying questions. Until now, there have been no contemporary studies with a tacrolimus- and MPA-based immunosuppressive therapy on this subject [48]. Current KDIGO guidelines recommend corticosteroids for the initial treatment of acute cellular rejection (1D) and suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode (2D) [39].

Steroid-resistant acute rejection. Data, even scarce and with only a limited number of patients ($n = 153$), are more recent and comparable for ATG in the treatment of steroid-resistant acute rejection [49, 50]. They essentially compared ATG to muromonab-CD3 (OKT3) in patients with a cyclosporine-/azathioprine-based regimen with comparable doses and time course. There was no difference for ATG compared to OKT3 for the risk of recurrent rejection up to 12 months after

therapy, but ATG was better tolerated [47]. More recently, Kainz *et al.* [51] reported, in a retrospective pseudo-randomized study using propensity scores, based on the Austrian registry, inferior long-term outcomes and graft loss for OKT3 compared with ATG after severe biopsy-confirmed acute renal allograft rejection in a cohort of 399 renal transplant recipients (368 ATG, 31 OKT3). They found in OKT3-treated patients a higher risk for functional graft loss [hazard ratio (HR) 1.79 (95% CI 1.06–3.02), P = 0.029] and actual graft loss including death [HR 1.73 (95% CI 1.09–2.74), P = 0.019]. Malignancies and infections were not different between groups in this study. Since then, no other studies have been published and OKT3 is no longer used for this indication.

Other therapeutic alternatives for steroid-resistant rejections [48] include mycophenolate mofetil [52–54], rituximab [48], intravenous Ig [55], plasmapheresis [48] and tacrolimus [56–59]. Since all these studies and case series were uncontrolled and performed before the modern era of immunosuppression and definition of rejection, it is difficult to transfer the results into the modern era.

To summarize, evidence-based data are scarce, old and do not allow using ATG as a first-line therapy in mild to moderate first acute rejection. Current KDIGO guidelines suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids and for recurrent acute cellular rejections (2C) [39]. No prospective data comparing ATG to other T cell–depleting therapies show its superiority in severe or steroid-resistant acute rejection. Moreover, none of the prospective studies has a sufficient period of follow-up to address long-term outcome and consequences of heavy immunosuppression. Yet, the bad tolerance profile of OKT3 in the absence of a statistical difference with ATG should at least persuade clinicians to use ATG preferentially in severe and steroid-resistant acute rejections. All in all, the risk–benefit balance has to be considered in terms of the risk of lymphoma (Epstein–Barr virus status), cumulative immunosuppressive load, propensity for infections, quality and prognosis of the graft, patient age and comorbidities, as well as patient preferences and compliance to treatment, when using a T cell–depleting therapy to treat severe and steroid-resistant acute rejections [48].

Acute ABMR

As pointed out, ATG can act on B cells and plasma cells through direct or indirect pathways. Most studies evaluating ATG in the treatment strategy of ABMR are particularly reported in mixed rejection forms including histological cellular and humoral features. One retrospective study has evaluated seven high immunological risk patients who developed early post-transplant acute ABMR [60]. The treatment consisted of an ATG-based regimen (mean dose 0.79 mg/kg/day for a median of 6 days), including steroid pulse therapy and plasma exchange. The authors showed a significant decrease in post-treatment creatinine with an improvement in graft function in six of the seven patients with this multimodal treatment. In general, until now we have had no data indicating that patients treated prophylactically with ATG induction experienced less ABMR or donor-specific antibodies. Despite induction with ATG in addition to other treatments, ∼44% of patients undergoing desensitization develop ABMR [61], indicating insufficient rejection prophylaxis under ATG. No prospective trial using ATG in ABMR is available, which would be important in light of the fact that novel pharmacotherapies targeting B and plasma cells or inhibiting the complement pathway have been developed to treat acute ABMR. Moreover, the absence of effectiveness of ATG on plasma cells *in vivo* and in desensitization protocols has probably decreased the interest for this molecule as a therapeutic option in acute ABMR [62, 63], as only a few US centres use ATG for treatment of ABMR [64] and eventually use ATG in case of mixed rejections. As outlined by a systematic review [65], evidence-based data supporting the efficacy of ATG are very limited, despite its use for decades. Some data suggest its potential efficacy in a combined treatment regimen with plasmapheresis for ABMR prevention for pre-sensitized patients [66]. Hence, ATG could be combined with other treatment modalities in ABMR associated with severe TCMR. KDIGO recommendations suggest treating antibody-mediated acute rejection with plasma exchange, intravenous Ig, anti-CD20 antibody and lymphocyte-depleting antibody alone or in combination with or without corticosteroids (2C) [39]. Nevertheless, until now, no clear benefit has been demonstrated using combination strategies with anti-CD20 antibody [67], and some combination therapy in the treatment of ABMR seems to be at higher risk of infection-associated death, particularly when rituximab and ATG are combined [68].

In conclusion, ATG is not a first-line treatment for ABMR because of its poor *in vivo* effect on B cell biology and the lack of evidence-based trials showing its efficacy in this indication. Nevertheless, ATG might be considered in patients with TCMR-associated acute ABMR, provided that infection prevention and monitoring is provided because of the higher risk of infection-associated death when combined with anti-CD20 therapy.

ATG AND LONG-TERM OUTCOMES

As pointed out, ATG have several short- and long-term side effects, including a higher risk of opportunistic infections, cancer and post-transplant lymphoproliferative disease [30, 36–38], although the latter is currently debated with regard to most recent data [69]. These risks are inevitable and have to be weighed against the benefits: in many cases of severe rejection, there are no evidence-based alternatives and the risk of graft loss outweighs the risk of overimmunosuppression. However, in case of rejection prophylaxis or treatment of TCMR, less toxic alternatives exist and different studies have suggested potential long-term toxicity of ATG. Meier-Kriesche *et al.* [70] reported in a retrospective registry-based study an elevated cardiovascular mortality in renal transplant recipients having received polyclonal anti-lymphocyte globulins, pointing out that intense immunosuppression may either accelerate atherogenesis or have a deleterious influence on the evolution of atherosclerotic lesions. Ducloux *et al.* characterized ATG-induced prolonged CD4 T cell lymphopenia as a potential immunological marker of overimmunosuppression in renal transplantation

[71–73] and subsequently showed its relation not only with atherosclerosis progression [74], but also with cardiovascular death [15]. Mechanisms underlying the involvement of ATG-induced prolonged CD4 T cell lymphopenia on atherosclerosis progression could be hypothesized from other populations with prolonged CD4 T cell lymphopenia. Survivors of the Hiroshima and Nagasaki nuclear bombs developed a prolonged CD4 T cell lymphopenia and were also reported to experience a higher incidence of myocardial infarction [75]. The analysis of T cell subsets revealed a poor renewal of naïve cell subsets and an oligoclonal repertoire resulting in dysfunction of anti-infectious immunity [76]. The long-term T cell pool renewal is made of a majority of memory CD8 T cells [77] with a simultaneous increase in biomarkers of inflammation (C-reactive protein and IL-6) [78]. The same clinical and immunological observations have been reported in HIV-induced CD4 T cell lymphopenia [79]. Moreover, chronic exposure to pathogens (CMV) in this population may lead to immunosenescence [80].

Features of immunosenescence have been reported in chronic kidney disease and are thought to be a consequence of accumulation of uraemic toxins and chronic exposure to dialysis, resulting in chronic immune activation and exhaustion [81, 82]. Yet, kidney transplantation and renal function recovery are not systematically associated with an improvement in immunosenescence features [83]. ATG has been identified as one of the main factors contributing to accelerated immunosenescence after renal transplantation [83].

More recently, Couvrat-Desvergnes *et al.* [1] explored the impact of ATG-induced SSD on kidney allograft outcome in a retrospective study including 889 first kidney graft recipients with ATG induction. SSD is the consequence of natural or ATG-induced antibodies directed against the xenogenic 'heterophilic' epitopes of ATG, in particular the Neu5GC antigen. This foreign antigen is a sialic acid (glycolyl form of neuraminic acid) that humans are incapable of synthesizing from the acetylated form, Neu5Ac, following the mutation of cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH) [1]. The formation, circulation and deposits of immune complexes in different organs are responsible for the clinical symptoms reported in SSD. In this study, SSD was defined by a combination of arthralgia and painful temporomandibular joint/trismus and accounted for 86 patients (9.7%) of the ATG-treated patients. SSD-positive patients were younger and risk factors associated with the development of SSD were young donor, young recipient age and transplantation before 1990. Although SSD was a relatively infrequent event, the authors demonstrated a lower long-term allograft survival in patients who experienced SSD, The differential death-censored allograft survival for 86 SSD-positive patients was −2.5, +3.1, −4.6 and −10.4% at 5, 10, 15 and 20 years, respectively, post-transplantation compared with 803 SSD-negative patients. Although no differences in anti-ATG and anti-Neu5Gc IgGs before transplantation or within the first year were observed between groups, SSD-positive patients had a significantly higher serum titre of anti-ATG and anti-Neu5Gc IgGs in late serum samples (more than 4 years post-transplant), suggesting a persistent deleterious long-term effect of anti-ATG immunization. This could suggest that SSD and anti-Neu5Gc IgG antibodies are either a trigger for induction of an inflammatory status or a marker of a strong immune-responder phenotype, as illustrated by a higher prevalence of acute rejection episodes in this group. In addition, a potential direct deleterious effect on the allograft of anti-Neu5Gc IgGs in ATG-primed individuals was hypothesized.

Uptake and incorporation in human tissues of non-human dietary sialic acid has already been reported [84]. Neu5Gc-positive endothelial cells (ECs) of the allograft endothelium could bind anti-Neu5Gc antibodies, resulting in chronic inflammation of graft vasculature. Indeed, the authors showed that living, fresh, uncultured human ECs could express substantial amounts of Neu5Gc on their cell surface and, moreover, that *in vitro* interaction of anti-Neu5Gc IgGs with their EC corresponding targets increases EC transcripts expression of vascular adhesion molecules and pro-inflammatory cytokines, suggesting involvement of the nuclear factor κB pathway in their potential pathogenicity [1].

To summarize, this study not only pointed towards potential risks of late allograft loss in ATG-induced patients who experienced SSD, but also explored SSD-related potential pathobiology that could lead to vascular allograft damage secondary to anti-Neu5Gc antibodies. The authors demonstrate an *in vitro* relationship between titres of anti-Neu5Gc antibodies and EC transcripts but could not confirm a higher expression of planted Neu5Gc in allografts of SSD-positive patients. These results need to be confirmed in larger studies and, though interesting, it should be emphasized that SSD remains a relatively infrequent complication, particularly with regard to the current indications and shorter period of ATG administration.

CONCLUSION

ATG remains an interesting and powerful tool to prevent and treat acute rejection in renal transplantation, particularly in highly immunized patients. Nevertheless, its polyclonal composition and its long-term consequences have been only partially explored. Furthermore, no data have been published to determine clearly the optimal dosing scheme and more prospective long-term data are needed to better understand the benefit–risk balance [47]. Recent data suggest a potential impact on long-term immunological recovery, which was associated with lower patient and allograft survival in some patient subpopulations. These data need to be confirmed in larger multicentric prospective studies along with a better and rigorous assessment of efficacy and toxicity in combination with current standard immunosuppression (tacrolimus and mycophenolates). Even less is known about the differential clinical impact of the two available ATG formulations. Thus, a careful individual risk–benefit assessment should always precede the use of this potent immunosuppressive drug [85, 86]. Future directions should focus on identification of immunological standardized biomarkers that could be routinely determined before transplantation and are capable of assessing the risk associated with the use of depleting cell antibodies as induction therapy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest with regard to this review.

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FULL REVIEW

Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative—a position paper

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ABSTRACT

Renal osteodystrophy (ROD) is a heterogeneous group of metabolic bone diseases complicating progressive chronic kidney disease (CKD). Bone biomarkers and bone imaging techniques may help to assess bone health and predict fractures in CKD but do have important inherent limitations. By informing on bone turnover and mineralization, a bone biopsy may help to guide prevention and treatment of ROD and its consequences. According to a recent survey conducted among European nephrologists, bone biopsies are performed rather exceptionally, both for clinical and research purposes. Obviously, clinical research in the field of ROD is threatened by vanishing clinical and pathological expertise, small patient cohorts and scientific isolation. In March 2016, the European Renal Osteodystrophy (EU-ROD) initiative was created under the umbrella of the ERA-EDTA CKD-mineral and bone disorder (MBD) Working Group to revitalize bone biopsy as a clinically useful tool in the diagnostic workup of CKD-MBD and to foster research on the epidemiology, implications and reversibility of ROD. As such, the EU-ROD initiative aims to increase the understanding of ROD and ultimately to improve outcomes in CKD patients.

Keywords: biomarkers, bone mineral density, chronic renal failure, hyperparathyroidism, renal osteodystrophy