Thromboembolism—Another Threat to the Polymorbid Patient with Vasculitis?

High Incidence of Venous Thrombotic Events among Patients with Wegener Granulomatosis: The Wegener’s Clinical Occurrence of Thrombosis (WeCLOT) Study. Ann Intern Med 142: 620–626, 2005

Patients with Wegener’s disease are known to suffer from a wide spectrum of pathology resulting from inflammatory lesions of small and medium-sized arterial vessels. Indeed, the definition of Wegener’s disease is based upon the localization of the typical lesions in the arterial vessels (1). A recent, prospective, observational, cohort study, a spin-off from a multicenter, randomized, double-blind, placebo-controlled, treatment trial on the use of etanercept in 180 patients with Wegener’s granulomatosis yielded an unexpected but clinically important observation. Such large studies are always good for surprising observations. In this case, Merkel et al. (2) found an impressively high frequency of deep venous thromboses and pulmonary emboli. The events were assessed prospectively using a rigorous and valid protocol. Although no concurrent control group was assessed, an impressively high excess frequency of venous thromboses and pulmonary emboli was documented in the patients with Wegener’s disease compared with informative, large, prospective series published in the literature concerning the healthy population (3), patients with rheumatoid arthritis (placebo arm of an etanercept study), patients with systemic lupus erythematosus (4), and patients with a history of venous thromboembolic disease (5).

The study of Merkel et al. (2) longitudinally followed patients with Wegener’s granulomatosis who had no evidence of active infection upon enrollment and who had active disease according to the Birmingham Vasculitis Score for Wegener’s Granulomatosis (BVAS/WG) (6), i.e., a score of 3 or greater. If clinical observation pointed to a venous thrombotic or embolic event it was confirmed (or refuted) by diagnostic studies such as ultrasonography, impedance plethysmography, ventilation/perfusion scanning, CT angiography, or other measures.

The observed incidence rates are indeed impressive. During follow-up for up to 24 mo, covering 228 person-years of observation, 16% of the patients with Wegener’s granulomatosis had venous thrombotic or embolic events at some time. Of these 7.2% had had a history of venous thromboembolic events before enrollment and 8.9% had first-time events in the course of the Wegener’s Granulomatosis Etanercept Trial (WeGET) trial. Risk factors such as bed rest, etc., were not reported, but the tight association with evidence of active Wegener’s disease at the time of the event or within 2 mo before the event, found in 81% of the patients, suggests a role of an inflammatory insult to the vasculature. Patients with thromboembolic complications tended to be older (mean age 57 versus 48.6 yr in patients without such complications). Importantly, length of hospitalization and proportion of patients hospitalized did not differ, nor did use of aspirin.

The first question that arises is obviously whether there is something unique about Wegener’s disease. The observed frequency of 7.0 per 100 person-years is definitely higher than the incidence of 0.31 first venous thrombotic or embolic events per 100 patient-years that had been reported in a healthy male Swedish population of similar age in whom events were carefully ascertained over 30 yr of follow-up (3). How does the incidence compare with other inflammatory autoimmune diseases? In the Hopkins Lupus Cohort study, venous thromboembolic events had been ascertained prospectively (4). The incidence was 1.0 per 100 person-years and in an observational cohort of 1271 prospectively followed patients with rheumatoid arthritis in an etanercept study, the incidence was 0.26 per 100 patient-years.
years. Even in the high-risk population of patients with a history of venous thromboembolic events who are known to have a high risk of recurrent events, an incidence of no more than 7.2 per 100 patient-years was observed in the placebo group of the randomized controlled trial of Ridker et al. (5). In this study the efficacy of low-dose warfarin for secondary prevention had been investigated.

So in Wegener’s granulomatosis the observed rate is higher than in other autoimmune diseases and is equivalent to that observed in patients with a history of venous thromboembolic events.

The findings are of interest with respect to underlying pathophysiology and patient management.

First, although so far investigations in patients with Wegener’s granulomatosis had almost exclusively focused on the involvement of the arterial and capillary branches of the vascular tree, the study of Merkel et al. (2) clearly points to some important pathology of the venous system as well. In the absence of histologic documentation it is difficult to comment on the underlying mechanism, but it is of interest that Woywodt et al. (7) found circulating endothelial cells, which obviously had sloughed off the vascular intima, denuding the basement membrane and exposing circulating blood to a prothrombotic surface. Obviously it is impossible from this observation to clarify whether these cells originated from the arterial or venous tree, but if the venous vessels were also involved this might provide a potential explanation. Furthermore, it might explain why venous pathology had largely escaped notice so far, as such changes might be quite subtle.

Second, the observation raises important points concerning the clinical management of these patients. Given the elevated, although not catastrophic, frequency of this complication and the potential risk of anticoagulation in the presence of active arterial lesions, the authors wisely refrained from advising routine anticoagulation. It is appropriate, however, that they recommended heightened awareness of the risk of thromboembolic complications, which may easily be misdiagnosed as alveolar hemorrhage or hemoptysis from necrotizing pulmonary nodules.

References
Kiellin/Chordin-Like Protein—A Novel Pathway to Prevent Renal Fibrosis?

Kiellin/Chordin-Like Protein, a Novel Enhancer of BMP Signaling, Attenuates Renal Fibrotic Disease. Nat Med 11: 387–393, 2005

Since the classical observations of Schainuck et al. (1), Risdon et al. (2), and Bohle et al. (3), it has been known that interstitial fibrosis in the kidney is more predictive of the risk of progression than the frequency and severity of glomerular lesions. An important, although possibly not the only, mechanism leading to interstitial fibrosis is epithelial to mesenchymal cell transition (4–6)—a concept which had originally been received with a dose of skepticism because at the time it was widely believed that tubular epithelial cells are terminally differentiated. The evidence that has accumulated by now, however, leaves little doubt that this type of transition does indeed occur. The spectacular versatility of stem cells in adopting or changing differentiation pathways helped remove intellectual barriers to accept the concept of transdifferentiation. Epithelial to mesenchymal cell transition is a final common pathway of progression in response to a broad spectrum of insults such as ischemia, hypoxia, inflammation, etc. It implies that the tubular cells lose the epithelial phenotype and acquire fibroblast-specific characteristics such as fibroblast specific protein 1 (7), matrix metalloproteinases 2 and 9, interstitial type collagen, and others (6).

As all important biologic processes, epithelial to mesenchymal transition is tightly regulated by numerous positive and negative regulators. Such multiplicity indicates that nature adheres to the philosophy of “not putting all of one’s eggs into one basket.”

In the control of signaling relevant for renal fibrosis, mainly two members of the TGF-β superfamily are involved (8), interacting with receptors of different receptor superfamilies and using different intracellular signaling pathways. These comprise the positive regulator TGF-β and the negative regulator bone morphogenetic protein 7 (BMP7): TGF-β promotes and BMP7 prevents renal fibrosis and scarring. Specifically, the TGF-β–driven profibrotic effect is directly antagonized by BMP7 (9). Such a reciprocal relationship suggests that a delicate balance must be maintained.

What do we know about BMP7 and the kidney? BMP7 is important in the embryonic development for the establishment of the dorsal/ventral pattern in invertebrates and vertebrates. In the kidney, it is necessary for branching and differentiation of tubules. In the adult organism, high doses of BMP7 attenuate, abrogate, or even reverse renal fibrosis in different models of renal damage (5,9–11). It is of interest to the clinical nephrologist that for this reason clinical studies on the efficacy of BMP7 in renal disease are currently underway. Parenthetically, BMP7 also ameliorates certain aspects of renal bone disease (12).

A further level of complexity in the regulation of epithelial to mesenchymal transition has recently been identified, i.e., the trap proteins (8). These are proteins that trap the ligands in the extracellular milieu. Activation of the BMP7 receptor causes phosphorylation of the intracellular signaling substances Smad1, Smad5, and Smad8, thus interfering with the nuclear programs coding for proteins necessary for epithelial to mesenchymal transition. The trap proteins that interact with the ligands may either inhibit or amplify the effect on their signaling pathways. For BMP, an entire flock of negative, i.e., inhibitory, trap proteins is known, including noggin, chordin, short gastrulation (Sog), twisted gastrulation (Tsg), gremlin, follistatin, and others (13,14). They bind BMP and prevent contact with their receptors (15).

It is here that the kiellin/chordin-like protein (Kcp) described by Lin et al. (16) enters the picture. In contrast to the aforementioned proteins, Kcp doesn’t inhibit the action of BMP7, but is actually the first protein to amplify it. It is a secreted protein with 18 cysteine-rich signaling domains and is most homologous to Xenopus kielin (17). Kcp is thought to act as a paracrine promoter of BMP7 actions by elevating the intracellular concentration of the signaling molecule Smad1. It binds to BMP7 and enhances binding to the type I receptor of BMP7.

What experiments did Lin et al. do to provide evidence for beneficial renal effects of the Kcp?
Kcp knockout mice were fertile and viable. This finding is remarkable in view of the fact that BMP7, the action of which is amplified by Kcp, has an important role in tubulogenesis, and suggests that there is some redundancy of control mechanisms. The renal effects of Kcp became evident, however, when the Kcp knockout mice were exposed to two types of renal injury. In the model of unilateral ureteral obstruction, renal interstitial fibrosis was seen earlier and was more intense in the kidneys of Kcp knockout than in wild-type mice. Kcp expression, as well as levels of the BMP7-dependent signaling molecule Smad1, were upregulated in the obstructed kidney of wild-type mice, but were not demonstrable in the obstructed kidneys of knockout mice. With some time delay, expansion of the interstitial area as well as accumulation of collagen I were seen as well. So interfering with the action of BMP7 by removing the BMP7-activating molecule Kcp increased the severity of renal interstitial fibrosis. In addition, in the folic acid model of acute tubular necrosis, higher mortality and more severe renal scarring were seen in Kcp knockout mice, illustrating that the observation can be generalized to include different kinds of renal damage.

Why are these findings of interest to the nephrologist? Despite the enormous progress achieved by blockade of the renin–angiotensin system and by other interventions to interfere with the progression of renal disease, these measures are not uniformly effective and there is still a desperate need for additional modalities of intervention. One such strategy may in the future be BMP7. It will then be important to identify factors that increase or decrease the efficacy of BMP7. For instance, it is conceivable that polymorphisms or conditions which increase or decrease the availability of Kcp determine the effectiveness of BMP7. We should also know which factors, e.g., renal disease or reduced renal function, modulate the availability of Kcp. In this context it is of interest that Lin et al. found increased Smad1 levels in the kidney contralateral to the obstructed one—possibly as a result of increased "workload."

Time will quickly tell whether the authors struck a gold mine or only chaff. My bet would be the former.

References

Steroid Maintenance Therapy after Transplantation—Quo Vadis?

Opelz G, Döhler B, Laux G; for the Collaborative Transplant Study Group

Since the seminal studies in the pioneer era (1), steroid treatment was regarded as an essential element of immunosuppression in the postoperative as well as in the maintenance phase after renal allograft transplantation. Very early on there had been concerns about the numerous long-term side effects, including the potential contribution to excess cardiovascular complications (2), the high rate of infections (3), and, more recently, the increasingly high rate of diabetes mellitus (4,5) as well as osteoporosis, osteonecrosis, cataract, weight gain, obesity, and dyslipidemia. Nevertheless, despite the pioneer efforts of some courageous nephrologists trying to administer less steroids (6), and in the maintenance phase frequently even no steroids, most nephrologists felt that the risk of rejection after withdrawal of steroids outweighs any benefit from lowering the rate of side effects. After the introduction of more potent immunosuppressants, Ponticelli et al. had repeatedly argued that steroids can be discontinued in the maintenance therapy of many graft recipients (7). The acceptance of this view was very mixed: the retrospective data of the Collaborative Transplant Study (CTS) documented that this approach was tried in no more than 10% of patients 1 yr after transplantation. Skepticism found further support in the results of the meta-analysis by Kasiske et al. in mostly short-term trials. He published in this journal (8) that after steroid withdrawal the risk of rejection was higher by 14 to 40%. In the study of Hricik et al. (9,10), acute allograft rejection episodes were indeed more frequent when steroids were avoided from the time of transplantation or withheld at some time after transplantation, but with the important qualification that patient or allograft survival was not adversely affected. In contrast, a Canadian study by Sinclair (11) with a prospective multicenter design had shown that patient survival was significantly lower in patients in whom steroids had been withdrawn. In this study, however, steroids were withdrawn remarkably early at 3 mo after transplantation and the difference between patients continuing or withdrawing steroids did not hold up when it was corrected for confounding factors.

These results led to a cautious and skeptical attitude among most nephrologists. Against these results, however, stood the retrospective data of the CTS. In 12,000 renal graft recipients on cyclosporine, alone or combined with azathioprine, 5-yr patient and graft survival rates were higher, and, in contrast to the above studies, not lower, compared with patients on triple drug therapy including steroids (12). It was possible to argue, however, that retrospective data are
not immune to bias. Against this background, and in view of the grave consequences of erring on either side, a controlled study was clearly indicated.

The optimal solution undoubtedly would have been a randomized controlled trial, but a consensus conference convened by Opelz opted against this solution, not in the least because of the adverse results of the preceding Canadian study (11). The second best solution was adopted, i.e., a prospective follow-up of low-risk patients with renal allografts (and a relative small cohort of patients with cardiac allografts) in whom steroids were gradually withdrawn no earlier than 6 mo after transplantation. The comparator group was deliberately composed of graft recipients with lower baseline S-creatinine (which, if anything, would make it more difficult for patients in the steroid withdrawal group to end up with better outcomes). These control patients were matched for a number of relevant parameters such as age, gender, race, donor age, HLA mismatch, etc.

The long-term results in 1110 cadaver renal graft and 450 cardiac graft patients from 43 centers are indeed impressive. The 7-yr renal graft survival was 6.6% better after steroid withdrawal (81.9 ± 1.1% versus 75.3 ± 1.2%; \( P = 0.0001 \) in matched controls) and patient survival was also 4.5% better (88.8 ± 1.5% versus 84.3 ± 1.0%; \( P = 0.0016 \)). The better graft survival was not an artifact resulting from better patient survival, because death-censored graft survival was better as well (91.8 ± 1.3% versus 87.9 ± 1.0%; \( P = 0.0091 \)). A similar benefit on graft survival was seen in heart recipients (76.2 ± 2.4% versus 66.9 ± 1.7%; \( P = 0.0008 \)).

In contrast to the above studies (8,9,11), the rates of acute rejection episodes and chronic renal graft dysfunction did not differ between patients receiving steroid-free and steroid-containing maintenance therapy. The protocol allowed for administration of steroids when they were thought to be required according to local established protocols, but 58.6% of the renal and 44.3% of the cardiac allograft recipients never required steroids.

As for the steroid side effects, somewhat surprisingly the number of patients requiring de novo antihypertensive therapy did not differ between the groups, presumably indicating that in the days of cyclosporine therapy the contribution of steroids to BP elevation has become minor. However, significantly fewer patients without steroids developed total cholesterol concentrations >300 mg/dl. New cases of osteoporosis and cataracts were not significantly different, but this may have been confounded by differences of prevalence at baseline and of cumulative steroid doses. Indeed, in patients in whom withdrawal of steroids was begun earlier, fewer cataracts were observed.

In good agreement with previous, uncontrolled, single-center experiences (7,13), the main finding is that in a large proportion of kidney and heart graft recipients, steroids can be withdrawn when certain provisos are respected in suitable, low-risk patients: when the start of withdrawal is delayed beyond 6 mo, when the rate of withdrawal is gradual, and when patients are well-supervised to allow resumption of steroids for acute deterioration of renal function should a rejection episode supervene. Of particular importance is the demonstration that this procedure is safe in the long-term as documented by no differences in 7-yr renal function despite previous observations to the contrary (14).

Therefore, delayed slow steroid withdrawal should not be tried in every graft recipient, but in a large proportion of patients it is feasible and safe with respect to graft function and beneficial with respect to patient survival, presumably because of a more favorable cardiovascular risk profile.

References
