Editorial

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UDCA prophylaxis for post-transplant PBC recurrence prevention: Time to change practice

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Recurrence of primary biliary cholangitis (PBC) after liver transplantation is an increasingly commonly recognised problem. It was originally described in 1982 by Neuberger *et al.*[1] Following this original description there have been a number of studies reporting it to occur in approximately a third of grafts.[2–5] In contrast to the management of PBC in the non-transplant population, where there has been significant recent progress and consensus as to the treatment approach, there has been, to date, no consensus as to how we should approach treating or, ideally preventing, disease recurrence post-transplant. In this issue, Corpechot and colleagues present unique data from the Global PBC Study Group that strongly suggest that ursodeoxycholic acid (UDCA) started at the time of transplant is highly effective at reducing the risk of disease recurrence.

This study is important for two reasons. The first, and obvious, important aspect of the study is that it gives us clear guidance that we should be using UDCA as a preventative step in all patients with PBC undergoing liver transplantation. Focus has previously been on commencing UDCA once recurrence has been confirmed rather than as a preventative measure. Commencing UDCA at that point has been shown to improve biochemistry but not survival.[6] This is probably not surprising given that the 'horse has already bolted'. Corpechot and colleagues present a retrospective cohort study of 780 patients transplanted for PBC between 1983 and 2017 in 16 centres. The median follow-up period was 11 years. The primary outcome measure was histologically confirmed recurrence of PBC. The use of histology to confirm disease recurrence is key given that autoantibodies typically remain positive after transplant for PBC regardless of recurrence status, and liver blood biochemistry abnormality can, for obvious reasons, be difficult to interpret post-transplant. The study participants were part of the broader Global PBC Study Group cohort that has provided several key recent findings relating to the clinical phenotype and outcomes in PBC. Of the study participants, 190 (24%) had received prophylactic UDCA following transplant. Across the 780 participants, 233 (30%) had histologically proven PBC recurrence. The recurrence rate at 10 years of follow-up was 31%.

Given that graft and patient survival in liver transplantation for PBC compare excellently to other indications, the traditional view has been that recurrent disease is not a significant clinical problem. Some studies have suggested that recurrence does not impact on graft or patient survival.[4,7] The Global PBC Study Group have, however, recently published data challenging this view and suggesting a significant impact from recurrence.[8] Corpechot and colleagues demonstrate, again, that recurrent PBC is not the benign process that it was once thought to be, with hazard ratios for graft and patient non-survivals with recurrence of 1.93 and 1.96, respectively. Of the 60 grafts that were lost, 24 (40%) were related to recurrent PBC. The study was not designed to be able to capture patient-reported outcomes. UDCA prophylaxis was associated with a highly significant reduction in recurrence risk on multivariate analysis (hazard ratio 0.41, 95% CI 0.28–0.61; p <0.0001). The 10-year recurrence rate was 37% in the non-UDCA group but only 18% in the preventative UDCA group. Interestingly, the study also confirms the previously made finding that tacrolimus as an immune-suppressant agent is associated with an increased rate of disease recurrence whilst cyclosporine was associated with a reduced rate.[2,5,9] The authors advocate using cyclosporine instead of tacrolimus as routine immune suppression for patients undergoing transplantation for PBC. The observation that UDCA prevents the onset of PBC recurrence, whilst tacrolimus predisposes to it, is fully compatible with the ideas of Beuers and others that the origin of PBC lies with a disturbed biliary microenvironment and resulting changes to the biliary epithelium, rather than a primary immune process.[10] This raises the obvious question as to the potential value of emerging anti-cholestatic drugs of increased efficacy, such as obeticholic acid and bezafibrate, in the prevention and treatment of recurrent PBC.

It is also interesting to note that this study showed that younger age at diagnosis with PBC or at time of transplant was associated with a decreased risk of recurrent disease, although this was no longer significant on multivariate analysis. This is in contrast to the paper by Montano-Loza *et al.*,[8] also utilising the Global PBC Study Group dataset, which showed younger age to in fact be a risk factor for recurrence. It is now well-established that patients who are diagnosed at a younger age have more aggressive disease and poorer outcomes with higher rates of

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interface activity and ductopaenia.[11] It would seem logical to think that those with more aggressive index disease may be at higher risk of recurrence and this is an area that needs further evaluation.

This study is also important for a second reason. It has given us an answer to a clinically important question that would otherwise simply not have been answerable. Well-designed, double-blind placebo controlled clinical trials are the gold standard for clinical evidence. As a cohort study, the study by Corpechot and colleagues could be regarded as providing lower quality evidence (and will, in the future, no doubt be judged as such in guidelines with graded evidence criteria). PBC recurrence is, however, a relatively uncommon complication of a relatively uncommon procedure (transplantation) in a rare disease (PBC has a prevalence of below 50/100,000 population; the standard definition for rare disease). Furthermore, recurrence rates only become appreciable after at least 5 years. To undertake a formal clinical trial of UDCA and its actions on disease recurrence would probably need every transplant centre across Europe to participate, and would take at least 10 years. This is not possible and such a trial will therefore never happen. The data provided by Corpechot *et al.* are not perfect (prophylactic UDCA use was centre-based and is not the only practice variable between centres, opening the way to potential confounders). The analysis is, however, detailed, the finding clear cut and, crucially, that finding supports the *a priori* hypothesis that UDCA is most effective when given at the earliest possible point in the disease course in PBC (and there is no earlier feasible point than the day of transplant for recurrent disease onset!). On that basis, the findings are the most robust that are ever likely to be feasible in answering this important question – thus, they should influence practice.

There is, though, a broader point. The question of recurrence of PBC post-transplant and its prevention by UDCA is, self-evidently, not the only live question about how to manage rare disease situations. Internationally, there is a huge focus on rare diseases and their optimal management. Furthermore, as with commoner disease types, the field of rare diseases is increasingly exploring stratified therapy approaches. Time and again, the issue of whether conventional trials are even possible in these rare disease subvariants crops up. The challenge of trials being "undoable" has the capacity to really slow progress for patients with rare diseases. Even in commoner disease areas, the conventional trial model is becoming increasingly challenging because of the costs and complexity. There is, therefore, a growing interest in the potential for different therapy effectiveness evaluation models, including the use of "real world data". Although rooted in a research project, the Global PBC Study Group data on UDCA and PBC recurrence are actually a really good example of the value of the "real world data" approach to answering key questions of great importance to patients that are not answerable using conventional trial methodologies. One barrier to the approach and its roll out in the future will be the reluctance of regulatory bodies, who typically require high quality clinical trial evidence, even when that evidence is impossible to obtain in practice. The saying "don't let the perfect be the enemy of the good" comes to mind. What would be really useful in fields such as PBC (followed in short order by primary sclerosing cholangitis and autoimmune hepatitis) would be a dialogue with regulators as to what types of real world data might be regarded as acceptable, and the "ground rules" as to required data curation quality. One issue that will be important in any future move to "real world data"-based intervention evaluation will be the effectiveness of approaches for collecting adverse event data. Understanding the safety of an agent is a fundamentally important part of the clinical trial model, with levels of data capture typically far in excess of normal clinical practice. Our confidence in recommending the use of UDCA for PBC recurrence prophylaxis, without gold-standard clinical trial evidence, is bolstered by the outstanding and long-established safety profile of the drug. This will not be the case with all, or even many, of the drugs evaluated using this approach in the future.

The key messages from this paper are simple. Recurrent PBC is an important problem that impacts around one-third of patients with PBC undergoing liver transplantation. The risk of death or organ loss is halved by prophylactic UDCA started immediately after transplant with no apparent risk and minimal cost. This should now become standard clinical practice.

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Authors' contribution

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Supplementary data

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