**Patient Consultation about a Trial of Therapeutic Plasma Exchange for Complex Regional Pain Syndrome**

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Short title: PPI on TPE in CRPS

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**Abstract**

Background: Complex Regional Pain Syndrome (CRPS) is a severe post-traumatic chronic pain condition affecting distal limbs, for which few effective treatments exist. CRPS is listed in the 2016 ASFA guidelines as an indication for plasma exchange treatment, but patient perspectives are lacking.

Methods: We convened a ‘patient and public consultation exercise’. Supervised by a Clinical Ethicist, the case for using therapeutic plasma exchange (TPE) was presented by a researcher and two TPE experts to five patients with severe, longstanding CRPS and to one relative. Discussions were recorded and transcribed.

Results: Participants supported the technology’s use but expressed concern that the small trauma of repeat cannulations of CRPS unaffected limbs might theoretically cause a spread of the condition, a risk which requires highlighting when taking consent. For a preliminary trial, the participants proposed to include no less than 10, preferably 20 participants. They suggested that the threshold for a decision to conduct a definite trial based on preliminary trial results should be set no higher than 1/5 patients achieving >30% pain reduction in the preliminary trial, with half of these responders achieving >50%. The use of sham-TPE, and a long trial duration (1 year) of a definite, parallel trial was considered acceptable, provided patients would be offered voluntary swap to the other trial arm at the end of the main trial period.

Discussion: These results provide pertinent patient views about TPE treatment which can inform both clinical consultation and consent procedure, and the design of future trials.

**Introduction:**

The revised, 2016 ASFA guidelines include for the first-time Complex Regional Pain Syndrome (CRPS), a highly painful and distressing chronic pain condition, as an indication for therapeutic plasma exchange (TPE),1 but reports on patient perspectives about this treatment are lacking.

CRPS is usually triggered by limb trauma and is characterized by severe pain and sensitivity perceived in distal limbs, along with limb-restricted autonomic, motor, bone, and skin abnormalities.2 Patients’ quality of life is amongst the lowest in any medical condition,3 however most cases will improve spontaneously or with rehabilitative treatment. About 15%-20% of patients will be left with persistent pain after 1.5 years, and are then unlikely to improve quickly (‘persistent CRPS’).4 For these patients, multidisciplinary management is indicated5.

Invasive neuromodulation involving implantation of an electrical pulse-dispensing lead close to the spinal cord or dorsal root ganglia can meaningfully improve symptoms in about half of these patients6,7; low-dose ketamine infusions, either on an outpatient basis over 10 consecutive days8 or with continuous infusion over 5 days9, can provide temporary pain relief, albeit with significant side effects.

For many patients, unfortunately, no effective pain relieving treatment exists.

Patients in this group experience relentless pain. They increasingly seek amputation of their limb, but there is considerable risk for a return of CRPS in the stump, and for additional painful complications.10

The condition’s inclusion into the 2016 ASFA guidelines was driven by the publication of reports describing the identification of specific anti-autonomic serum autoantibodies associated with CRPS,11,12 successful establishment of an immunoglobulin G passive transfer model,13 and the apparent efficacy of plasma exchange in a substantial proportion of treated patients.14-16 The treatment recommendation was graded as ‘Grade III’, indicating that the ‘optimum role of apheresis therapy is not established, and decision making should be individualized.’ The supporting clinical evidence for this recommendation was derived from two case series and two case report, with overall n=42 patients treated through four different centers.

Prospective trials, and ultimately an RCT can help further clarify the efficacy and effect size of this novel treatment approach, however there are no reports available on patient perspectives about apheresis treatment for CRPS, or the design of clinical trials. To better understand how patients might consider TPE, while balancing effects with side effects or inconvenience, and how they would view a fit for purpose trial design we convened a ‘patient and public involvement’ (PPI) exercise.

**Methods**:

We arranged a directed discussion, where the TPE intervention itself, the reasons underpinning its consideration, and the design of a planned clinical trial were described to a ‘patient and public’ panel, in the context of potential advantages and disadvantages of this technology; panel feedback was sought throughout the exercise. An independent Clinical Ethicist ensured fair and balanced information-provision, and intervened where needed to ensure that panel members fully understood what was put to them.

The panel consisted of 5 patients with severe persistent CRPS and the wife of one of the participating patients. These patients had previously expressed an interest to be involved in CRPS-related projects; three of the participants had been under AG’s care in the past, and two participants and the relative had been under the care of a different centre and had previously been involved in a CRPS guidelines project.5 As a consultative exercise, analogous to a focus group, statistical significance is not sought, so involvement of six participants provides a convenient group size consistent with qualitative, opinion-gathering methodology.  Research ethics approval was not required for this PPI exercise as the UK Health Research Authority (HRA) requires applicants to explain how they have involved patients and the public in protocol development prior to application to a research ethics committee. The HRA advises that, “Good practice would be to include involvement before REC review, to improve the ethical acceptability of research and inform the ethical review process.” 17 Participants were reimbursed for their travel from internal funds. All participants gave written consent to audio recording of the event, subsequently transcribed by JB.

*Outline of the initial panel proceeding*: welcoming the participants, the ethicist (JB) set the stage by explaining the rationale for the PPI exercise. This was followed by the pain specialist’s (AG) clarification of the reason for trying TPE in CRPS (because the condition appears associated with functionally active autoantibodies, and TPE can remove autoantibodies). A cartoon, developed previously for outreach activities to non-specialist audiences, explained issues around the presumed pathogenic action of autoantibodies. Two clinical TPE specialists working for the main regional TPE service (SJ and TC) explained the procedure and answered technical patient queries. Together with AG they also explained the different possible venous access routes.

**Results**

Condition: Workshop participants were asked: ‘since CRPS is a non-destructive condition, setting it apart from potentially destructive conditions such as pemphigus, how much more careful do we have to be about using invasive therapies such as TPE?’.

In response, all participants clarified that they considered CRPS as ‘destructive to the mind’. As one participant observed, “*I think it is destructive, not maybe in the medical way, but it is. I mean it’s wrecked my life. So I’d see it as a destructive thing, you know, it might not actually destroy your cells as such but it destroys your life and your want to be here really and I’ve met a lot of other people similar.”*

Intervention side effects: Workshop participants worried that TPE might cause CRPS-spread through repeated cannulations. TPE side effects other than CRPS-spread were generally classed as mild, with acceptable proportionality to the potential benefit of relieving CRPS-related pain. The consensus in the panel was that the potential for relief of CRPS symptoms trumped other considerations: *“You know, I don’t know where you lot stand, but I’ve been in the position where I’ve wanted to cut the limb off. Yeah? We’ve all done that, so this is where we’ve been with our minds.”* The greatest concern for participants, was the risk of any treatment exacerbating existing CRPS symptoms or causing CRPS in a new location. However, when asked whether they regarded the risk of CRPS exacerbation as a wholly unacceptable risk (a ‘deal-breaker’) the consensus was that they would still assess the risk-benefit ratio on a case-by-case basis, and would take into account the severity of symptoms at the time of considering a new intervention. As one participant put it, *“My CRPS at the moment is just in one part of my body. Probably like everyone else here I’m petrified of any injury, wouldn’t consider a tattoo or anything that might damage me and make this response spread. So, for me, I probably wouldn’t consider the treatment you’ve just outlined because I feel I’m coping while some of you here have got much worse day-to-day* *impact than I have, so that threshold is very much to do with how much the condition affects your day-to-day function.”* Another reported having proceeded with implantation of a spinal cord stimulator, despite a concern about surgically induced CRPS: *“I was slightly worried about that when I had that put in, but I was just so desperate at the time. And I’ve now got a lot of back pain but it’s not CRPS, it’s from the machine, but I understand where you’re coming from.”* The consensus of the panel was articulated by a third participant who commented that, *“It’s like any type of research isn’t it? You’re going to get people with that condition who’ll try anything, and others a bit more sceptical because they’ve tried so much and it hasn’t worked and it hasn’t been as effective as they’d expected it to be. I think we need to look at this research and see its pros and cons. Like any other research, it’ll have a negative effect on someone and it will also have a positive effect on other people. By doing this [PPI exercise], I think it opens up for people to understand the implications of doing this research but, as in all research, you have to go through this process, don’t you?”*

Trial outcome measures and trial design: workshop participants considered progression criteria for a proposed, staged TPE trial design. It was suggested by AG to have a first open part, and then, if efficacy is suggested by the open results, a randomized controlled part. Efficacy would be ascertained by the number of patients responding, and the extent of their responses. Patients considered neither a proposed number of patients to be openly treated initially (n=6, followed by another 6 patients if there is a response in some of these 6), nor a proposed minimal required pain relief after treatment of >50% for at least one of these 6 patients to be acceptable. They agreed that a lower responder rate than 1/6 and a more moderate treatment response than >50% pain relief should be considered. All participants thought that a 30%-40% pain reduction would incur a substantial improvement in quality of life in their condition.

In negotiations with the academic investigator, in which health economical issues were also considered, the following parameters were posited: inclusion of 10 patients into an initial open study, where 2 patients would need to have at least 30% pain relief, and 1 of these would have at least 50% pain relief to justify progression to the RCT. Some workshop participants suggested that at least 20 patients should be tested openly, in order not to miss a relevant TPE effect.

Venous access: Sham TPE requiring same venous access as active TPE in a future RCT was considered acceptable. For an *outpatient-based* TPE study designed to enroll patients with acceptable peripheral venous access on ultrasound screening, panel participants, having received information about risks and benefits of different venous access protocols, expressed a view regarding access escalation in cases of peripheral access failure. Participants regarded escalation to the femoral vein (groin), and jugular vein (neck) to be acceptable, but not to the subclavian vein (chest); patients with failed jugular vein access would need to be withdrawn.

Panel participants rated the inconvenience of receiving repeated TPE, through repeated de-novo peripheral access as rather low, with acceptable proportionality to their condition: *“I don’t think it’s that much inconvenience. If you suffer from CRPS, doing something like that isn’t an inconvenience. Doing that for,* *even if it’s twenty times, y’ know it’s not an inconvenience to be honest.”* They rated the level of invasiveness of the intervention as acceptable, including when compared to spinal cord stimulator treatment.

Study duration: when asked about the duration of a blinded parallel RCT, considering 6 months’ versus 12 months’ duration where, after the end of the parallel phase, participants in both groups would be offered one treatment cycle of ‘true’ TPE, workshop participants did not have a preference for either time period. They suggested that most trial participants would accept a 12 months RCT duration if this was deemed better suited by the investigators.

Caveat: patients participating in the PPI exercise highlighted that they would tell other patients through social media if they thought any intervention would provide them with pain relief, even if this was during a trial.

**Discussion**

The use of immune modulation treatment for (non-destructive) chronic pain conditions is a novel approach and little is known about patient perspectives on the appropriateness and proportionality of using such treatments. We conducted a PPI event with five patients and one patient’s relative to gain initial insight into patient perspectives on TPE treatment, and the design of a prospective trial.

Patients considered potential TPE side effects and risks as mild, however, they expressed concern about the risk of developing CRPS at a cannulation site, or of any research intervention or novel treatment increasing the usual CRPS pain. However, even the risk of CRPS exacerbation was regarded as potentially acceptable depending on the extent of the risk and the severity of the symptoms of the particular patient making the decision. Currently the risk for these complications are not known. Although there are no reports on the triggering of CRPS by small skin biopsies18 which require an injury to the skin that is larger than the cannulae used for TPE, stimulation of the venous intima by the TPE cannula might have additional triggering potential. How far repeated peripheral cannulation can be a trigger for CRPS-spread in patients with CRPS remains to be established. It is also important to consider that in a RCT, with repeated exchange treatments in the active group the presumed pathogenic antibodies will be reduced although no such reduction occurs in the sham group; this might, at least theoretically increase the risk for cannulation triggered CRPS-spread in the sham group when compared to the active group. The ‘sham’ intervention might thus have potential to actually cause harm.

Patients discussed and dismissed originally proposed ‘proof of concept’ trial-participant numbers. They instead suggested that 10-20 patients be treated openly, the pain-relief ‘response’ threshold be reduced from suggested 50% to a mix of 30% and 50%, and a ‘response rate’ with these criteria of 1 in 5 deemed acceptable. As it can be challenging to decide the sample size in a proof of concept trial where no data from earlier trials exists, patient perspectives could be considered to underpin decision making. Ultimately this PPI exercise would have accepted an even higher number of patients treated for each responder; however, patients were content to negotiate these numbers acknowledging real-world information on health economics (in the absence of predictive factors, the intervention may become unaffordable to a public healthcare system such as the UK National Health Service (NHS) if the number of responders is low), and burden (repeat-cannulation of a large number of patients for a rare positive response). Notably, recent research results indicate that although treatment-refractory persistent CRPS is rare (estimated <1:2000/population) delivery of trials with up to 200 participants is feasible.19,20

Since the duration of pain relief following TPE would be an important outcome in a RCT, thus requiring long trial durations, and, equally, as data about any incremental treatment effect from repeat treatment would be advantageous, patients considered that a 12-months duration of such a trial would be acceptable provided that, as planned, all participants would be offered optional swop to the other treatment arm at the end of that time.

*Strengths* of this consultation include the involvement of patients suffering from persistent CRPS who would be potential candidates for inclusion into a proposed future trial, and the participation of an independent clinical ethicist, who ensured balanced and understandable presentation to the panel. The presenters were experts in their respective fields.

*Limitations* are that the panel was small; there may have been selection bias, e.g. for people who are comfortable speaking in a group, and this panel may think differently about TPE than other patients. Since the pain specialist and the TPE specialists have seen positive TPE responses in the past,14 they may have unintentionally steered patients towards certain answers. We were, however, rather indifferent to several possible outcomes from this exercise, including a decision not to proceed with a trial if patients found the intervention too invasive; conducting a trial for a rare condition assessing an intervention that is not considered acceptable to the target group would render recruitment time-consuming and might be futile. Further, outcomes were often unexpected, including the proposed acceptable response rates and trial duration. It would have been informative to ask patients how important it would be for them to know whether they were seropositive for pain-sensitising autoantibodies before TPE was considered; of note though, preliminary evidence has suggested that most patients in this group are seropositive.13

**Conclusions**

In this initial consultation exercise, patients with persistent CRPS considered plasma exchange treatment an acceptable treatment technology for their condition and suggested specific trial design elements to the conduct of proof of concept, and definite trials. These results may support clinicians considering trials on TPE and other immune-modulating treatments for non-destructive chronic painful conditions.

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