Editorial

Management of hard-to-heal diabetic foot ulcers: local use of autologous leucocytes, platelets and fibrin multi-layered patches (LeucoPatch)

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Hard-to-heal diabetic foot ulcers (DFUs) represent a clinical challenge for physicians and healthcare systems worldwide. It is estimated that approximately 77% of DFUs heal within 1 year in specialised tertiary care European hospitals (1,2). DFUs are associated with impoverished quality of life and a high cost for healthcare services (3).

The Wound Healing Society guidelines advocate advanced wound therapies for DFUs, should the latter be not reduced in size by ≥40% following standard therapy for 4 weeks (4). So far, such advanced therapies include negative-pressure wound therapy (5), hyperbaric oxygen therapy (6), ultrasound-assisted debridement (7), new wound dressings (8,9), different types of dermo-epidermal skin substitutes (10), granulocyte-colony stimulating factor (11), as well as autologous stem cells (12).

In this context, a recent multi-centre, international, observer-masked, randomised controlled trial (RCT) by Game *et al.* (13) has provided favourable results on the use of autologous imnune cell, platelet and fibrin patches (LeucoPatch). This was applied to the surface of the wound in subjects with diabetes and hard-to-heal DFUs (13). The RCT was carried out in 32 specialised diabetic foot clinics in the United Kingdom, Denmark, and Sweden. Patients with a DFU reduction <50% after a 4-week run-in period were randomised to either pre-specified good standard care alone (137 patients) or care plus weekly application of LeucoPatch (132 patients) (13). The primary outcome was the proportion of healing ulcers (defined as complete epithelialisation) within 20 weeks and remained healed for 4 weeks. Forty-five (34%) of 132 ulcers healed within 20 weeks in the LeucoPatch group *vs.* 29 (22%) of 134 ulcers in the standard care group [odds ratio (OR): 1.58, 95% confidence interval (CI): 1.04–2.40, P=0.0235] within 20 weeks (13). Median time to healing was 72 days [interquartile range (IQR), 56–103 days] in the LeucoPatch group and 84 days (IQR, 64–98 days) in the standard care group (P=0.0343), time to healing was shorter up to 12 weeks in the LeucoPatch group than in the standard care group [hazard ratio (HR): 1.709, 95% CI: 1.071–2.728, P=0.0246] (13). Major or minor amputations, episodes of clinical infection, antibiotic use or serious events showed no difference between the two treatment arms (13). Importantly, adverse or serious adverse event rates did not differ between the two groups. This holds true for incidence of anaemia in LeucoPatch-treated patients, despite repeated venesection (13).

The RCT by Game *et al.* (13) has important strengths. First, it focused on hard-to-heal DFUs. Secondly, all investigators offered standard-of-care treatment using pre-specified criteria, maintained through regular scientific meetings. Moreover, the target number of participants was finally recruited, and patient retention at the end was very

high (13-15). A limitation was that it was not possible to mask either the participant or the researcher to treatment allocation, but the primary outcome was assessed by a blinded independent observer and backed up with digital imaging (13).

Unfortunately, there are currently few robust RCTs on care products for DFUs. Platelet preparations have been suggested as adjunctive therapies, but the clinical evidence for their efficacy remains limited and inconsistent (16,17). A previous multi-centre pilot study has shown that the leucocyte patch is well-tolerated, easy to use and holds therapeutic promise (18). Unlike other treatments based on autologous blood, this local therapy has a compact, three-layered structure: a layer with a high concentration of fibrin, a layer of concentrated leucocytes and a layer of concentrated platelet, which exhibit different chemotactic, mitogenic and proliferative properties (18,19). The new RCT (13) has provided strong additional evidence on the efficacy and safety of LeucoPatch.

Nevertheless, it is necessary to perform RCTs for other types of DFUs. Indeed, Game *et al.* (13) included non-infected DFUs, according to the Infectious Diseases Society of America (20), without critical leg ischaemia. Most DFUs were >1 cm^2, superficial and on the forefoot (13). Moreover, very large DFUs (>10 cm^2), those with very marked ischaemia and patients with severe renal disease were excluded (13). These DFU characteristics do not accurately reflect everyday clinical practice. Still, the median number of recruited ulcers in each centre was similar to a recent RCT of another dressing acting on the activity of matrix metalloproteinases (sucrose octasulphate dressing) to accelerate wound healing in patients with neuroischaemic DFUs (Explorer) (8). In the Explorer trial, in contrast to the Leucopatch trial (13), neuroischaemic DFUs were defined by the University of Texas Diabetic Wound Classification system as IC (ischaemic, non-infected superficial wound) or IIC (ischaemic, non-infected wound penetrating to tendon or capsule) and large ulcers were included (1–30 *vs.* 0.5–10 cm^2). In both RCTs, patients received an off-loading device and at wounds were debrided at the investigator's discretion and following the International Working Group of the Diabetic Foot guidelines (21).

We now know that more than half of DFUs become infected (22) and the prevalence of osteomyelitis in DFUs is currently 66.7–70.4% in specialised diabetic foot units (23,24). Game *et al.* (13) reported no differences in the incidence of diabetic foot infection between both groups (24 events in the Leucopatch group *vs.* 20 events in the standard care group). Furthermore, only 3 ulcers (2%) in the standard of care group and 6 (5%) in the LeucoPatch group penetrated to the bone. A recent case report shows that leucocyte platelet rich fibrin could be useful in the treatment of DFU with osteomyelitis, calling for a dedicated RCT (25).

Based on the study by Game *et al.* (13), production of LeucoPatch is fast and, and its application is very convenient. Certainly, patient satisfaction was not evaluated, but there were very few dropouts. Moreover, a cost-effectiveness analysis will be required. The optimal treatment duration also needs to be better ascertained. Of note, healing was faster in the intervention group during the first 12 weeks, but not thereafter, tempting us to ponder whether LeucoPatch treatment might be terminated before complete wound closure (13).

In conclusion, the excellent RCT by Game *et al.* (13) has provided robust evidence in support of a new intervention based on fibrin, autologous immune cell and platelet patches in the management of recalcitrant DFUs. Their results are very promising. Accordingly, experience in other types of DFUs and cost-effectiveness analysis are highly welcome to increase the utility of this product for clinical practice.

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Footnote

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