

REVIEW

Vascularised Composite Allotransplantation – Basic Science and Clinical Applications

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Vascularised Composite Allotransplantation (VCA) is the top rung of the reconstructive ladder, offering ‘like-for like’ functional reconstruction for the most devastating tissue loss. There are established centres across Europe, the USA and Asia. Clinical outcomes now extend beyond 20 years. To-date over 130 upper limb and 37 craniofacial VCA’s have been performed, with encouraging graft survival and clinical outcomes. Beyond hand and face transplantation novel VCA’s have been performed including: functioning allotransplantation of neck organs, penis, uterus and skull and scalp transplants. Like solid organ transplant (SOT) patients, VCA recipients are submitted to the significant side effects of lifelong immunosuppression, however in this case surgery is considered life improving rather than life saving. As clinical feasibility is now well established research focus has shifted to improve the safety profile of VCA. This has included exploring strategies to enable early detection and treatment of acute rejection, defining and better understanding chronic rejection in VCA, and ultimately aiming to induce tolerance. The aim of this review article is to give a concise overview of the clinical and basic science advances in the field of VCA, with particular relevance to the orthoplastic surgeon.

Keywords: vascularised composite allotransplantation; reconstructive transplant; hand transplant; lower limb transplant; tolerance

Introduction

Vascularised Composite Allotransplantation (VCA), in carefully selected patients, allows excellent functional and aesthetic reconstruction after devastating tissue loss. The first reported VCA was an unsuccessful hand transplant performed in Ecuador in 1964 [1]. Subsequently, significant advances in immunosuppression and technical expertise lead to the world’s first successful hand transplant in 1998 and face transplant in 2005 [2, 3].

To-date there have been 130 upper limb and 37 craniofacial VCAs performed worldwide [4, 5]. There have also been numerous novel VCA’s reported, including: vascularised abdominal wall transplant (AWT), functional neck organs, vascularised knee joint, uterus, penis and skull and scalp transplants [6–11].

Long-term clinical outcomes are now a reality with follow-up exceeding 20-years in some cases. As clinical experience, technical skill and research have developed the indications for VCA have been further refined. The worlds first paediatric transplant in 2016 and VCA’s to reconstruct oncological defects have been testament to these expanding indications [7, 11–13].

Despite encouraging outcomes reported globally for VCA, the risk benefit equation remains finely balanced due to the requirement for life-long immunosuppression. Even with modern immunosuppression regimes, VCA patients, like solid organ transplant (SOT) recipients, are at a greater risk of: malignancy, infection, endocrine dysfunction and renal failure [13–15]. Several deaths have occurred [16–18]. Additionally, the majority of VCA recipients will experience one or more episodes of acute rejection and a small cohort have now shown signs of chronic rejection, including vasculopathy and delayed graft loss [19].

A number of controversial topics persist in the field of VCA and include: lower limb transplantation, multiple simultaneous transplants and paediatric transplantations [18, 20–24].

The aim of this review article is provide an overview of the current state of VCA in devastating extremity tissue loss, with particular relevance to orthoplastic surgeons, in both civilian and military centres.

Clinical applications of VCA

History

The technical feasibility of VCA can be traced back to origins of microsurgery and the accumulation of knowledge and skill following the first microsurgical anastomosis by Jacobson and Suarez in 1960 [25]. Parallel advances in the field of SOT also paved the way for VCA and date back to Joseph Murray’s first successful renal transplant between two identical twins in 1954 [26, 27]. This was followed by

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the revelation that renal transplantation could be achieved in non-identical twins using irradiation [28]. The following decades saw the first cadaveric renal allotransplant performed, refinements in immunosuppression regimes and the expansion of life saving SOT to other organs including liver, pancreas and small bowel. The first reported case of VCA in the literature was performed in Ecuador in 1964, lasting just two weeks in the absence of immunosuppression [29]. Thirty-four years later the first successful hand transplant was performed in France by Dubernard and colleagues (1998) [2]. This was the start of a rapid expansion in the field of VCA that later included the first successful face transplant, performed in France in 2005 [30, 31].

Upper Limb Transplantation

Loss of one or both hands has a devastating effect on independence and leads to significant physical and psychological disability [32, 33]. Upper limb transplantation helps address these issues by re-instating independence and dignity for patients with a lightweight, sensate, waterproof reconstruction not currently matched by prosthetics. Since the first hand transplant in Lyon, France in 1998 there have been 120 upper limb transplants performed world-wide in 74 patients [4]. The 2017 International Registry on Hand and Composite Tissue Allotransplantation (IRHCTT) presented encouraging results from 66 upper limb cases, with patient survival at 1, 5 and 10 years of 96.7% and graft survival of 86.6% at 5 and 10 years, similar to that of SOT [34].

All patients with surviving grafts regained protective sensation with 82% regaining discriminative sensation [35]. The majority of upper limb transplants recorded on the 2011 IRHCTT regained enough extrinsic and subsequent intrinsic motor function to return to work and undertake independent activities of daily living [35].

Historically, the American Society for Reconstructive Transplantation (ASRT) put forward a number of proposed contraindications to upper limb transplantation, that included: unilateral amputees with no evidence of significant functional, social or financial impairment as a result of their amputation, congenital and paediatric amputees [36]. A study by Mathes *et al.* in 2009, surveyed 474 surgeons regarding attitudes toward hand transplantation and concluded that most surgeons supported upper limb transplantation only as a solution for dominant hand loss or for bilateral amputees [37]. In reality, no universally agreed indications exist for upper limb transplantation and many of the modern contra-indications relate to individual patient suitability, both physically and psychological. As such, careful multi-disciplinary work-up for each patient is critical, with full consideration given to alternatives that could be achieved via conventional reconstructive methods [38].

Bilateral upper limb transplants have been performed since 2003 with good medium to long term results including return to work and patient satisfaction [39]. Encouraging results have been seen with more proximal transplants including those at a mid-humeral level, again showing return to work with useful elbow flexion and return of sensation [40]. The first bilateral paediatric

upper limb transplant was performed in North America in 2016 with short-term follow up showing independent toileting, return of sensation to light touch and some intrinsic muscle function by 7 months [13].

Integrated myoelectric prosthetic devices offer an alternative for some patients with devastating upper limb injuries. Currently, the functional outcomes and patient acceptability of upper limb VCA are not matched by that of prosthetic devices. However, research looking to decrease device weight, develop pattern recognition programmes and provide clinically applicable tactile and proprioceptive feedback is encouraging [41]. Improved prosthetic devices are likely to have a greater role in the management of upper limb injuries going forward.

Upper limb transplantation, in carefully selected patients, can be considered the gold standard orthoplastic reconstruction for devastating upper limb injuries, particularly in bilateral cases, not amenable to conventional reconstructive techniques [42].

Face transplants

Devastating craniofacial injuries from trauma or burns are often linked to psychosocial morbidity, social phobia and the development of substance misuse [43, 44]. Facial VCA can provide significant improvement in quality of life and function, and was first performed in France in 2005 [30]. Since then thirty-seven craniofacial transplants have been performed worldwide. There has been a rapid expansion in the complexity of cases performed from the original 'partial' mid-face transplant, to the most recent complex transplantation of ears, ear canals, tongue, scalp and bone [45]. Expansion in indications for face transplant have seen the worlds first 'acute face transplant' performed, and three facial transplants for blind patients [46, 47]. The first case of repeat transplantation of a face, as yet unpublished, was recently performed, in France, which has partially ameliorated concerns relating to 'life-boat' options in facial VCA cases [48].

Patient survival, as reported in the 2017 IRHCTT, is 96.2%, with 5 reported deaths worldwide [34]. Cause of mortality ranged from non-compliance with medication, to malignancy and death associated with combination transplantation [5]. Graft survival is 96.6% at 5 years [34].

A recent review by Pomahac and colleagues (2018) found satisfactory return of sensation at 8 – 12 months but that motor recovery lagged behind those initially anticipated for facial transplant [49]. Motor function returned between 6–18 months post operatively with the majority of patients able to breathe, speak, eat and drink after transplantation [5].

Face transplant is still in its relative infancy and has experienced encouraging short to medium term results. An international consensus on outcome measures and data recording is essential going forward as is stringent patient selection and postoperative psychological support.

Abdominal Wall Transplant

Vascularised abdominal wall transplantation (AWT) facilitates closure of the abdominal domain following multi-visceral (MVT) or isolated small bowel (ISB) transplant.

Difficulty in closure of the abdominal wall following such transplant procedures is reported in approximately 20% of cases. Loss of the abdominal domain is related to scarring from previous surgery, fistulae, sepsis and oedema of the newly transplanted organ [6, 50].

The first case of AWT in conjunction with ISB transplant was reported by Levi *et al.* in 2003 [50]. To-date approximately 35 full-thickness vascularised AWT have now been performed in conjunction with MVT or ISB transplantations [6]. Early reported outcomes, in this small field, have been encouraging with no reported mortalities and approximately 9 episodes of acute rejection [6].

AWT is a unique VCA as it is performed in patients requiring life saving MV or ISB transplants, with no additional immunosuppressive burden. As experience has grown with AWT the utility of the skin-containing transplant as an immunologic monitor has become apparent. Exploitation of this finding by the use of sentinel skin flaps in SOT is an exciting novel development.

Early reported success with AWT in the absence of additional immunosuppressive requirements makes it an appealing solution to closure of the abdominal domain. The future is likely to see more units seeking IRB approval to carry out such VCAs in conjunction with ISB or MVT and the expansion of AWT indications to include large hernias, trauma and tumours.

Lower Limb Transplants

Bilateral lower extremity amputation, especially transfemoral (TF) amputation, in civilian or military patients, can be devastating, leading to wheelchair dependence, loss of work and significant mental health morbidity [23]. Indeed, the LEAP study highlights that only 58% of patients returned to work 7 years after their amputation [51, 52]. The option to reconstruct an un-salvageable lower limb injury with a VCA is appealing but has traditionally been met with resistance due concerns around poor functional recovery, high-risk surgery and burden of immunosuppression. The on going debate in the field of VCA surrounding the risk: benefit ratio of lower limb VCA originates from the relatively poor functional results historically reported following lower limb replants [53, 54]. However, after reports of good functional outcomes of upper limb transplants worldwide, even those at a mid-humeral level, the concept of lower limb replant and the possibility of VCA were revisited [18, 31, 32]. Cavadas *et al.* (2009), in a single centre, reported encouraging results of 12 infra-popliteal replants over a 4 year period [55]. This work highlighted the technical feasibility of lower limb transplant and demonstrated the potential for encouraging recovery.

To-date, there have been 4 lower extremity transplants reported. The first, and only long term success, was performed by Zuker *et al.* in 2006 [24, 56]. In this unique case, a normal lower limb from a 3 month old ischiopagus twin, who was not going to survive, was transplanted successfully to her twin. Due to the immune compatibility no immunosuppression was required. Six years on the patient is mobilising with a brace, fully engaged in school with good motor and sensory recovery reported.

In 2011, Cavadas carried out the first bilateral TF lower limb VCA, with encouraging functional results (Tinnel's at the malleolar level, active knee extension and active plantar flexion) and ambulation between parallel bars at one year [21]. Unfortunately, despite encouraging short term results the patient developed a possible cerebral lymphoma at 2 years and the limbs had to be removed [22].

The final two cases of lower extremity transplant were performed in conjunction with other, simultaneous VCA's, both resulting in mortality. The third case was performed in Turkey in 2012, for a quadruple amputee and resulted in cardiac arrest and ultimately death at day 4 post operatively [18]. The fourth and final case, as yet unpublished, was carried out by Ozkhan in 2012 and included one lower extremity and bilateral upper extremity VCAs, leading to mortality at 5 months post operatively [57].

Lower limb VCA remains a widely debated topic in the field of VCA, especially when performed in conjunction with additional VCAs in one operation. Significant morbidity and mortality have prevented any further attempts at lower limb transplant since 2012. However, technical feasibility and encouraging short term results have been demonstrated [21]. On going research is warranted to improve peri-operative care and resuscitation, immunosuppression and nerve regeneration to improve the safety profile of such major operations. Despite the set backs presented, the potential utility of lower limb VCA in both civilian and military patient populations is great, and as such a number of proponents of lower limb VCA persist [23]. The possibility of performing more distal transplants as a starting point to re-introduce lower limb VCA and to gather further data for research has been proposed [22].

Other VCAs

A number of pioneering VCAs have been performed that, despite being a small number of cases, have been landmarks in the field:

En bloc allotransplantation of neck organs

In 2015, a Polish team performed the first allotransplantation of neck organs, including: larynx, trachea, pharynx and oesophagus, functioning thyroid and parathyroid glands, hyoid bone with the anterior bellies of the digastric muscles, sternohyoid muscles, anterior cervical wall and a skin paddle [7]. The recipient was a 34 year old male, with a previous renal transplant, who underwent a total laryngectomy and radiotherapy for a T3N1 squamous cell cancer of the larynx and was fully tracheostomy and gastrostomy dependant prior to VCA. Early outcomes indicate normal endocrine homeostasis and independent speech, swallowing and breathing.

Skull, Scalp, Pancreas and Kidney transplant

In 2015, a 55-year old male underwent skull and calvarial VCA, in Texas, for an aggressive, recurrent leiomyosarcoma of the skull and scalp with associated full thickness osteoradionecrosis. The patient also underwent concurrent kidney and pancreas transplant with no adverse outcomes on graft function or survival reported to-date [11].

Allogenic vascularised total knee joint transplants

Experimental transplantation of vascularised total knee joints was reported as early as 1908. In the absence of microvascular techniques or immunosuppression they were universally unsuccessful [8]. In 1996, a German team, lead by Hofmann reported the first successful allogenic, vascularised total knee joint transplant for severe, post-traumatic knee defects. In total, 6 cases were performed with encouraging short-term results, including ambulation. However, long-term follow up published in 2007 highlighted only one of six grafts survived. Graft lost was attributed to; infection ($n = 1$), non-compliance with immunosuppression ($n = 1$) and late rejection ($n = 3$) [58]. Total knee transplants have subsequently been stopped.

Uterus Transplant

The first successful uterine transplant, as a treatment for absolute uterine infertility, was published in 2014 [59]. To-date over 42 uterine transplants have been performed in 11 countries with 12 reported live births [9, 59–61]. The first 11 of these were from living donors, however the first live birth from a deceased donor was reported in 2018 [62]. Recently, the first successful live birth was reported in the United States [63]. This is a unique, but still largely experimental VCA, that has shown encouraging early results. The procedure does require immunosuppression, however, the ability to remove the VCA, via a hysterectomy, at the time of birth minimises some longer-term risks. As with all new areas of VCA, collaborative international data reporting and dissemination of results is essential. Initial clinical trial data with, 4–5 years follow up, is expected to be published between 2023 and 2025, by the Swedish group, lead by Mats Brännström [64].

Penis Transplant

To-date there have been 4 successful penis/penis scrotum transplants performed worldwide, in three centres in the United States and South Africa [10, 65–67]. The first case of penile transplant was performed in China in 2006, but was removed 14 days later due to significant psychological distress experienced by the recipient [68]. The next successful penile transplant was performed in South Africa in 2014, for a 21 year old male who was rendered aphalic following complications of a ritual circumcision [10]. Reports at 24 months include successful erections from week 3, sexual intercourse from week 5 (against medical advice) and pregnancy at 3 months, unfortunately leading to a stillbirth. Early reports from the first USA case are also encouraging with partial sensory recovery at 7 months, spontaneous erection and improved psychological parameters [65].

Military VCA

Over the course of military conflict in the Iraq and Afghanistan, advances in trauma care pathways and technology led to an annual improvement in survival, often with more devastating injuries than previous wars [69]. Despite advances in body armour, vulnerable areas such as the extremities, pelvis and head and neck were still exposed

to blast trauma and resulted in higher rates of amputation and craniofacial trauma than previously reported [70, 71].

VCA offers an appealing opportunity to help military veterans with significant composite tissue loss, not amenable to conventional reconstruction. The United States Department of Defence has shown significant interest and support to both pre-clinical and clinical VCA projects in the USA. Currently they help finance the successful facial transplantation programme at Brigham and Woman's Hospital in Boston, with a potential pool of eligible military veterans estimated in excess of 200 [72]. Nearly one third of face transplants to-date have been performed because of ballistic trauma leading to a great deal of expertise in dealing with this indication for veterans potentially requiring this treatment [73].

In a recent study Fries *et al.* (2018) summarised the worldwide experience of upper limb transplantation in military recipients [74]. To-date there have been 6 cases performed in the US, India and Poland. Three patients had excellent return of function, two have no published follow up and one US soldier had to have his hand transplant removed due to non compliance. They noted that despite excellent pre-morbid fitness and rehabilitation motivation, the potential downsides of high functional demands, concomitant mild traumatic brain injuries and possible PTSD may exclude some veterans [74].

Recently, successful combined penis and scrotum transplant was performed for a war veteran, at Harvard in The USA [67]. VCAs for even larger pelvic defects may be an opportunity for veterans with devastating pelvic trauma.

Basic Science in VCA

VCA is now a worldwide clinical reality. The dramatic expansion in reconstructive transplantation has seen a shift in research priorities; from establishing clinical feasibility, to improving functional outcomes and decreasing the burden of immunosuppression and inducing tolerance.

Improvements in our understanding of VCA immunosuppression in conjunction with lessons learnt from parallel SOT research has provided a number of tools to improve, but not negate, the risk - benefit profile of lifelong immunosuppression in VCA. The long term clinical sequelae of immunosuppression are well known and include diabetes, infection, malignancy, metabolic disturbance and renal failure [75]. Mortalities related to long term immunosuppression in VCA have now been reported [76].

Many of the VCA units around the world use immunosuppressive protocols in line with that of SOT, although no universal guidelines for VCA exist at present.

Induction protocols typically consist of either polyclonal (Anti-thymocyte Globulin) or monoclonal (Basiliximab or Alemtuzumab) antibody preparations followed by maintenance protocols using standard triple immunosuppression with Mycophenolate Mofetil (MMF), Tacrolimus and Prednisolone [77, 78]. A notable exception to this is seen with ISB/MVT and concomitant AWT using Tacrolimus monotherapy only after induction [6].

The use of 'steroid sparing' dual immunosuppression allows complete withdrawal of corticosteroids after

a period of weaning with the ultimate goal of reducing side effects such as hypertension, hypercholesterolaemia and metabolic derangement. In an early series of 5 face transplant patients by Diaz-Siso *et al.* (2015), successful conversion to a steroid sparing regime, after a mean of 4.8 months, with manageable episodes of rejection was reported [79]. However, in direct contrast to this, a recent report of the development of chronic rejection in a VCA using a steroid sparing regime questioned the impact of such a protocol on long-term graft survival and patient morbidity [80].

SOT research has highlighted the clinical advantages of converting calcineurin inhibitors (Tacrolimus) to mTOR inhibitors (Sirolimus) for long term graft maintenance for improved graft and patient survival [81]. The adoption of this approach for long-term maintenance in VCA has now been seen, especially for those experiencing renal impairment using traditional protocols. However, conversion to mTOR inhibitors may also lead to increased episodes of rejection with unknown effects on graft survival and function [82].

Current immunosuppression protocols in VCA have translated to graft survival of over 87% for upper limb transplant and 97% for face transplant [34]. However, the majority (>84% for face transplant and >85% for upper limb) of patients who receive a VCA will experience at least one episode of acute rejection [83]. The common clinical features of acute rejection include swelling and erythema [84]. A useful clinical classification was put forward by Cendales *et al.* (2006) that helps classify signs of acute rejection and promote uniform data reporting and collection [85].

VCAs are unique in the field of transplantation as they contain multiple tissue types (skin, bone, muscle), with skin thought to be the most immunogenic [86]. The clinical utility of early signs of acute rejection being visible on the skin component of a VCA is the focus of on-going research. The role of the AWT as a sentinel skin graft leading to early detection and treatment of rejection for both VCA and underlying ISB/MVT has been demonstrated [87–89]. This may be translated to reduced morbidity by avoiding over immunosuppression. In combination with intestinal transplantation the addition of a VCA does not seem to increase the risk to the SOT; increase graft dysfunction or loss or increase donor specific antibodies [90].

This principle has led to the use of sentinel flaps to detect rejection in both VCA and SOT. Sentinel flaps are fasciocutaneous free flaps retrieved from SOT donors and inset into in a remote site of the recipient. Initially in facial VCA their intended purpose was to facilitate serial biopsies, away from the VCA, avoiding visible scarring on the craniofacial graft. They were described during the first face transplant in 2005 and a reliable correlation between signs of acute rejection on the sentinel flap and the VCA appears to exist [30]. It is worth noting not all inflammatory skin changes indicate rejection and infection and allergy must be considered [83]. On-going trials continue to see if there is utility for sentinel flaps to be used in non-VCA transplants such as ISB, pancreas, heart and lung. Visceral transplants are traditionally difficult to biopsy to

confirm rejection and challenging to monitor clinically; an easily accessible area of donor tissue with visual monitoring may have great utility.

Currently, VCA monitoring involves observation, serial biopsies and in some centres vascular imaging [80, 83]. Histological grading is according to the Banff 2007 working group skin containing composite tissue allograft classification. Assuming patient compliance with immunosuppressive medication, all episodes of acute rejection have been salvaged to-date. Most commonly, oral or intravenous steroids form the mainstay in rescue treatment. However, for steroid-resistant cases, ATG, Basiliximab or Alemtuzumab can be used. In addition 95% of cases reportedly use topical Tacrolimus or Steroid preparations for cases with evidence of rejection [78]. It remains to be seen what the effect of multiple episodes of acute rejection will have on long term VCA survival, however this has been associated with poorer long term outcomes to SOT [19].

Chronic rejection (CR) in VCA involves both skin and underlying vasculature leading to progressively impaired graft function and eventual loss [19]. A number of clinical cases of CR have emerged in both face and hand transplant [19, 91]. Currently there is much research interest directed toward understanding this complex phenomenon in VCA and to establish underlying pathogenesis and agree on recommended treatment algorithms [19].

Inducing tolerance in VCA

The induction of tolerance in VCA allowing rejection free acceptance of transplanted tissues without the need for immunosuppression, is the ultimate goal of both VCA and SOT research [92]. Removing the significant morbidity of life long immunosuppression and the risk of delayed graft loss due to chronic rejection would allow an unrestricted expansion of the field of VCA. Concurrent tolerance research in the field of SOT provides promise for translation into the field of VCA. Encouraging results have been presented in renal allografts with successful tolerance protocols now implemented in some centres, allowing complete withdrawal of immunosuppression [93, 94]. Similar strategies in liver transplantation has enabled rejection free survival of liver allografts in 20% of adult and 60% of paediatric recipients following withdrawal of immunosuppression [95, 96].

The most promising avenue for inducing a state of VCA tolerance appears to be establishing stable mixed chimerism [97]. This can occur when a patient's bone marrow is myeloblated and transferred alongside donor bone marrow [98]. A number of centres have utilised this process to reduce immunosuppression requirements in VCA. Indeed, the Pittsburgh team presented mid term follow up for upper extremity transplant and weaned patients to Tacrolimus monotherapy using a bone marrow, cell-based treatment protocol with infrequent skin rejection [99].

Inducing tolerance in VCA remains a unique challenge due to the antigenicity of the skin and multiple tissue elements transplanted [86]. Leonard *et al.* (2014) state: *“Reliably achieving tolerance of all components of a VCA, across a full MHC mismatch is a formidable challenge, to which mixed chimerism remains the most promising*

approach to date” [97]. Ongoing large animal research to establish safe, clinically applicable protocols for tolerance induction in VCA forms a key part of VCA research.

Conclusions

There has been an exponential expansion in the field of VCA over the past two decades. VCA has the potential to transform lives after devastating injury and allow re-integration back into society. The next two decades, for this young field, will refine the safety profile of toxic immunosuppression aiming toward the goal of inducing tolerance. As the number of VCA centres around the world increase, international research collaboration and agreement on definitions and protocols are essential.

For the orthoplastic surgeon upper limb VCA offers a sensible, lightweight functional reconstruction with encouraging long-term results, including at proximal levels. Some authors contend that this is already the standard of care treatment for bilateral hand loss [42]. The future role of lower extremity transplant for bilateral amputees, in military or civilian populations, although appealing, is currently on hold and requires further research and planning before this high stakes operation becomes a clinical reality. The success of novel VCAs in treating more ‘bespoke’ defects, of either traumatic or oncological aetiology, demonstrates the power of the technique, and suggests all practitioners of reconstructive surgery should be aware of its potential when faced with clinical cases that challenge conventional reconstructive practices.

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Author Contributions

Calum S. Honeyman

Substantial contributions as first author in writing and editing the paper at all stages, final approval and agreement to be accountable for all aspects of the work.

Charles A. Fries

Substantial contributions in the conception of article and as second author editing all drafts of the manuscript, final approval and agreement to be accountable for all aspects of the work.

Guarantor

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