Hand Transplant

Preliminary Results and General Considerations

Marco Lanzetta

Clinical results of hand transplantation are extremely encouraging. The vast majority of the operations performed in 8 centers around the world have shown more than satisfactory results both immunologically and functionally. The patient’s selection criteria must be very rigid and should include type and level of traumatic amputation, age of the patient, previous experience with prosthetic alternatives, psychological status, a complete informed consent. Hand transplantation can then be a valid solution for highly impairing deformities.

Summary
The clinic experience of hand transplant includes so far 19 cases, 6 of which are bilateral, for a total of 25 hands transplanted in 8 different centres around the world (Tab.1). The teams that have operated could count on multidisciplinary competence that included transplant surgery experts, reconstructive microsurgery and reimplants of body segments, immunology, clinical psychology, legal medicine, neurology, functional rehabilitation, bioethics.

The organisational aspect is extremely important for the preparation of a hand transplant program, as it is necessary to have a continuous coordination with the structures in charge of the donation and the organ transplant activities, and requires that many health and administrative workers remain on the alert.

The problems regarding hand transplants are partly similar to the ones that other types of transplant present, while others are unique because linked to the concept of function-saving transplant or life quality rather than life-saving transplant. In this sense, from a bioethical point of view, non life-saving transplants are justified only when they have a therapeutic purpose and are not just purely cosmetic. The evaluation of procedure benefits that will restore anatomic integrity to the individual and will increase the functional independence cannot ignore the possible risks linked to the immunosuppressive therapy.

Results and general considerations
The first transplants carried out and the results obtained give rise to various considerations that cover only some of the issues raised by:

Informed consent
It must be as exhaustive as possible and include all aspects of this new procedure, in order to allow a completely free choice of the patient. To make a decision, patients should be adequately informed about short and long term, known and less known risks and benefits, about the whole procedure, about working, social and family implications and about the rehabilitation period. All this should be done in a precise way, suitable to the cultural and social level of the patient.

Life quality transplants
This concept is very common in hand transplants, but it has already been widely introduced in transplants of mono-tissue organs such as the kidney or pancreas, where transplants do not exclusively intend to save an individual, but aim above all to improve life quality. Currently, most kidney transplants are carried out on patients
before dialysis. A kidney or pancreas rejection does not cause death, but the return to lower life quality conditions.

**Functional reconstruction transplant**

It is a logical and readily comprehensible innovation, when traditional procedures cannot be used (reimplant at the time of the trauma, autologous reconstructive transplant of compound tissues), because of obvious limits related to the dimensions of the lost part and to the complexity of the function that needs to be restored. This innovation is also a response to poor patient satisfaction after prosthesis, despite the improvement of technology in this sector.

**Differences from life-saving transplants**

With a life-saving transplant an irreversible rejection of the transplanted organ (heart) causes the patient’s death. Similarly, a very serious side effect forces the patient to face a new and progressively worsening disease, as the immunosuppressive therapy cannot be stopped in any way. With hand transplant, when a serious and unhealthy side effect is about to occur, the immunology therapy must be immediately suspended and, if necessary, the part reamputated. A state of tolerance following the immunosuppressive therapy’s discontinuation cannot be taken into account in life-saving transplants; in hand transplants it could be justifiable, also to prevent long term side effects, to interrupt the antirejection therapy at a fixed term, the rationale being the likelihood of tolerance resulting from a stable chimerism.

It is therefore reasonable to state that a non life-saving hand transplant is not even a potentially life-losing transplant.

The lack of side effects in patients subjected to hand transplant is another big difference which emerges over time. This can be explained by the fact that people who are waiting for a life-saving transplant (heart-liver) are usually in very poor health and therefore life expectancy is extremely reduced. Their debilitated organism does not possess the resources necessary to contrast the effects of a powerful antirejection therapy and therefore the risk of side effects is greater. On the contrary, patients subjected to hand transplant, despite their serious pathologic state due to deformity, possess the strength to allow immunosuppressive therapy.

**Immunological therapy**

By using combinations of immunosuppressing medicines in the postoperative immunologic therapy, it has been possible to reduce the dose of single components, in order to obtain a synergic effect and to subtract one or more of these medicines during the postoperative treatment. The results coming from worldwide series of monotissue organ transplants show a decrease of side effects alongside a better immunosuppressive effect. A first important fact emerging from the first clinical cases of hand transplant is that these medicines are able to control the antigenic skin activity very well, both in monolateral cases and where the transplanted skin covers a double area.

**Surgery**

As far as surgery is concerned, hand transplant is similar to an autologous reimplant carried out in a state of emergency after a traumatic amputation, usually at work. Technically speaking, however, there are significant differences that make it more complex. Firstly, one of the most important differences lies in the fact that the surgery team has to take a sample according to criteria reflecting the recipient’s clinical condition (amputation level, condition of stump, lack of skin tissue or skin dystrophy,
etc.). Secondly, whereas tissue dimensions, quality and physiologic age match in case of tissue reimplant, with a transplant a certain degree of diversity between the two parts has to be expected. This diversity must be minimised, by choosing a donor as far as possible compatible for age, limb dimensions, skin colour, sex, and general morphology. From a strictly technical point of view, a recently amputated forearm does not present all the difficulties of limb stumps, especially when the amputation took place many years before. In these cases a high quantity of fibrosis has to be expected, particularly in tendons and muscles, where the sliding surfaces are completely unrecognisable. Nerves inevitably present terminal neuroma, requiring more proximal resections of the nervous tissue to look for a better site. Our clinical experience (4 cases-5 hands) has taught us that during surgery it is always necessary to operate some variations or recombinations, especially regarding tendon sutures, sometimes through primary tendon transfers. Another important difference concerns the vascular axis. Whereas in acute (reimplant) cases their dimensions are equivalent and usually they do not require grafts, in a transplant the arteries must be identified much more proximally than the peripheral limit of the stump and of the skeleton. At the same time, vein size and capacity are poor. This therefore arguably implies the main difficulties in this kind of operation.

The nervous regeneration
During the period immediately following the first hand transplant, speculative comments not supported by evidence indicated how the impossibility of nervous regeneration in these patients made the transplant a purely technical act with no functional value. At present, the most promising aspect of hand transplant is the degree of nervous regeneration both on the sensitive and motor level. This is due to the evident capacity of a peripheral nerve to reactivate a distal growth if adequately stimulated from the periphery, which has already been clinically tested in the cases of toe transplant with a follow-up of some years. It is also due to the action of Tacrolimus neurostimulation, which combines immunosuppressive and neurotrophic actions due to the removal of some barriers inhibiting axonal growth.

Italian program of hand transplant
The Ministerial approval for the request of authorisation for hand transplant by the San Gerardo Hospital in Monza of the Milano-Bicocca University gave us the opportunity to give a substantial contribution to the world experience in this sector. The program consists of 5 cases in a period of 4 years. The selection criteria are extremely rigid and include:
- Loss of dominant hand or preferably both hands
- Age between 18 and 50 years
- A traumatic amputation at wrist level
- A motivated refusal of prosthetic alternatives, both aesthetic and functional
- The capacity to express full informed consent
- A stable psychological state
- Compliance with the period of postoperative rehabilitation

So far we have carried out two single transplants (dominant right hand), in two male patients aged 35 and 32. In both cases we waited for a highly compatible donor with the same morphology, age and hand dimensions. In both cases the donators were young, of the same sex and with identical hand dimensions, with no previous injuries or pathologies that could directly or indirectly invalidate hand function (arthritis, diabetes, skin diseases, congenital malformations).
The immunosuppressive therapy of the Italian protocol was completed in cooperation with the Department of Transplants of Ospedali Riuniti di Bergamo, combining Tacrolimus (FK506), Mycophenolate Mofetil (MMF) and steroids. The induction is carried out with monoclonal antibodies (Simulect).

Table 1: World experience in hand transplant

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<th>Centre</th>
<th>Single</th>
<th>Bilateral</th>
<th>Total hands</th>
<th>Program start</th>
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<td>2</td>
<td>5</td>
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<td>-</td>
<td>2</td>
<td>Jan 1999</td>
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<tr>
<td>Guangzhou</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>Mar 1999</td>
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<tr>
<td>Guangxi</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>Jan 2000</td>
</tr>
<tr>
<td>Innsbruck</td>
<td>-</td>
<td>2</td>
<td>4</td>
<td>Mar 2000</td>
</tr>
<tr>
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<td>-</td>
<td>1</td>
<td>May 2000</td>
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<tr>
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<td>-</td>
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<td>1</td>
<td>2</td>
<td>Jan 2001</td>
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<td>Bruxelles</td>
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