Adverse effects of intradermal allogeneic lymphocyte immunotherapy: acute reactions and role of autoimmunity

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BACKGROUND: Immunotherapy with allogeneic lymphocytes was introduced as a therapeutic option for selected infertile couples in different centres worldwide 20 years ago. It has been suggested for other indications as well, e.g., for pregnant women at risk of a child with Rhesus-D haemolytic disease, or as a vaccine which might reduce the receptiveness for HIV-1 infection. Here we report on our experience on adverse side-effects of intradermal lymphocyte immunotherapy (LIT) for infertile couples using partner’s lymphocytes. METHODS: Prospective 4 week follow-up of all couples from 2000 to 2003 for acute reactions (feedback 2587/3246, 83%). All couples treated between 1996 and 2002 received questionnaires after 2–3 years (feedback 1914/3041, 63%). RESULTS: Local reactions predominantly consisted of redness and itching for ~2 weeks. Systemic reactions could be attributed to LIT in 6–8%. Blister at the injection sites were characteristic of LIT but not dependent on the HLA class I mismatch status between cell donor and host. The incidence of autoimmune disease was 0.1%. Four patients developed thromboembolism in pregnancy which was not ascribed to antiphospholipid syndrome. CONCLUSIONS: Acute side-effects are comparable to those reported after intradermal vaccination for infectious diseases. Specific risks for anaphylaxis, autoimmune or graft versus host disease were not detected.

Key words: allogeneic lymphocyte immunotherapy/autoimmunity/graft versus host disease/HIV/Rhesus haemolytic disease

Introduction

Allogeneic lymphocyte immunization is a therapeutic concept which was proposed in 1981 (Beer et al., 1981; Taylor et al., 1981) and in the following years gained acceptance for treatment of women suffering from recurrent miscarriage. It was also adopted for couples who had been unsuccessfully treated in the IVF programme, and several variants of the procedure were developed. Lymphocytes were derived from HLA-different blood donors or from the husband and injected intravenously (i.v.), subcutaneously (s.c.) or intradermally (i.d.). A meta-analysis published in 1994 concluded that among the group of primary first trimester aborters who did not suffer from auto-immune disease the chance to conceive a child was raised by 8–10% (Recurrent Miscarriage Immunotherapy Trials Group, 1994). In our institute the intradermal method was established in 1985 following the schedule proposed by A. Beer. Our own data indicated that there was also some improvement for patients with recurrent implantation failure in the IVF programme. The pregnancy and birth rates were elevated by a quarter for embryo transfers in the first half year after lymphocyte immunotherapy (LIT) compared to the national registry of all German transfers (Kling et al., 2002a,b).

Nevertheless, LIT is not a first-line therapy and requires exclusion of other factors contributing to infertility. So the efficacy is still based on statistical analysis of an non-homogenous group of infertile patients, and as a consequence has been discussed controversially since the 1990s (Clark et al., 2001; Chaouat, 2003; Christiansen et al., 2004). A US trial even suggested an unfavourable outcome for couples with habitual abortions (Ober et al., 1999). It decisively influenced the issues of the current Cochrane review and the US FDA regulation (Scott, 2000; Center for Biologics Evaluation and Research, 2001). Nevertheless, the design of the study itself was a matter of debate (Clark et al., 2001). Moreover, concern on possible adverse effects of LIT, such as transfusion-related problems, autoimmune disorders or even cancer and gestational pathology was raised. Although several studies have partly addressed these aspects in the past, a detailed evaluation has not been published.

In recent years, LIT with paternal lymphocytes has been proposed as a therapeutic approach to prevent severe haemolytic disease of the fetus/newborn (HDFN) caused by fetomaternal Rhesus (D) discordance (Neppert et al., 1999; Lam et al., 2003). Allogeneic immune response to HLA antigens plays a complex role in HIV infection (Quayle et al., 2004). Since the 1990s, allogeneic LIT has been suggested as a component of a vaccine which might reduce the risk for acquiring an HIV-1 infection (Kiprov et al., 1994; Shearer et al., 1999).

The discussion on LIT outlined above shows that a comprehensive evaluation of possible side-effects is warranted. This survey focuses on the local and systemic reactions of i.d. LIT.
which can be observed within the first month as well as on possible signs of autoimmunity. In our experience, LIT has a distinct profile of possible risks which can well be outlined. Our results provide a basis for further considerations whenever the application of this method is taken into account.

Materials and methods

Patients

Couples were referred to our outpatients department from infertility clinics in Germany for repeated implantation failure in the IVF/ICSI programme or for recurrent first trimester miscarriage. Women who suffered from a systemic autoimmune disease or who already had detectable antipaternal HLA antibodies were precluded from treatment. On average the women were 33.7 years old (range 21–43 years). Seventy-five per cent of them had never been pregnant.

For HL A class I tissue typing we used the serological microlymphocytotoxicity method until 2001, later the sequence-specific oligonucleotide probe molecular typing method (SSOP) (Dynal RELIT™ SSO HLA-A,-B-Test; Dynal Biotech Ltd, Bromborough, UK). HLA class II typing was applied for couples who had identical class I antigens (Dynal Alliset™ SSP DR,DQ ‘low resolution’). Those who were also identical for class II were precluded from treatment.

Complement-dependent HLA antibodies against the partner’s lymphocytes were measured before and 1 month after LIT by the standard lymphocytotoxicity assay. The results were scored according to the Terasaki criteria. After staining of the target lymphocytes in the microwell tray with eosin, the percentage of cells injured is assessed under the microscope and scored as follows: 0 (no cells, 1 (1–10%); 2 (11–20%); 4 (21–50%); 6 (51–80%); 8 (81–100%); 9 (not readable). The background cell damage is assessed by a negative control (Hopkins, 2000). The quality of HLA antibody and antigen testing in our laboratory was assessed regularly for the Eurotransplant Organization, Leiden, The Netherlands.

In our experience additional tests for detecting non-cytotoxic HLA antibodies (e.g. flow cytometry) increase the sensitivity substantially but are not further discussed in this context.

Sera were routinely derived before and 1 month after LIT and stored at −21°C (−4°F). Antiphospholipid and anticardiolipin antibodies (IgG, IgM) (ORG 529, ORG 515; Orgentec, Mainz, Germany,) were tested in four patients who later developed deep vein thrombosis. Antibodies to the phospholipid–β2-glycoprotein complex as well as to cardiolipin or cardiolipin–β2-glycoprotein complexes were assayed respectively. For antiphospholipid IgM the threshold was 22 MPL-U/ml, for IgG 16 GPL-U/ml, for anticardiolipin IgM 7 MPL-U/ml, for IgG 10 GPL-U/ml IgM phospholipid antibody resp. IgG phospholipid antibody (ab) testing in U/ml, acc. to manufacturer calibrated against reference sera provided by E.N. Harris, Louisville, USA] bilirubin, SGPT (ALT), alkaline phosphatase (Ortho-Diagnostics, USA) were tested from these sera in 10 patients who showed exanthema after LIT.

Two weeks before LIT the partner was tested for HbsAg, HCV-Ab, HIV-1,-2 Ab and CMV IgG and IgM Ab.

Lymphocyte immunotherapy

Usually 50 ml, occasionally 100 ml, of heparinized blood were drawn from the male partner. The lymphocytes were separated under sterile conditions by Ficoll-hypaque density gradient centrifugation using normal saline for suspension. After two washing steps the cells were resuspended in 1 ml normal saline. After microscopic evaluation the suspension was given to the female partner by eight to ten intradermal injections at the volar side of one forearm. The suspension was not stored but applied 2–3 h after blood withdrawal. Four weeks later we tested for antipaternal HLA antibodies and recommended a further LIT if the test was negative.

Cell count

Prior to LIT the suspension was checked for its cellular contents using phase contrast microscopy after staining with eosin. The upper limit for thrombocyte contamination was regarded as 100 × 10⁶ cells, for erythrocytes 1.4 per 1 ml. If necessary, the number of thrombocytes was reduced by washing the suspension for a third time. Erythrocytes were lysed in hypo-osmolar saline and isotonic milieu was restored by adding 1.8% saline.

Prospective survey for side-effects

Between June 19, 2000 and December 31, 2003 (42.5 months), all patients consecutively received a questionnaire concerning the nature and duration of local and systemic complaints which they returned 4 weeks after LIT (short-term). We conducted 3246 cycles of LIT. In all, 83% (2587/3246) of treated patients returned the questionnaire: after the first LIT 85% (2168/2550), after the second LIT 76% (482/637), after three LIT 65% (35/54), after four LIT 40% (2/5). The majority of patients were treated for IVF failure (2451/2587, 95%), 136/2587 (5%) for primary recurrent miscarriage. Ten women of these had one live-born child with another partner. The IVF patients answered as often as the patients suffering from recurrent miscarriage (114/136, 84% versus 2054/2414, 85%). From 2003 on, patients added data on prescribed medication to the short-term questionnaires. This gave a clue concerning parallel treatments, e.g. for upper airway infections.

Moreover, all couples who attended our institute for implantation failure between 1996 and 2002 received a second (long-term) questionnaire 2–3 years later. Among other aspects, these patients were also requested to report on general health problems.

Statistics

The influence of LIT variables on local and systemic reactions was examined by χ²-test. P < 0.05 was considered significant.

Results

Reactions observed by the patients

Local reactions

During the first week after treatment an inflammatory reaction usually builds up which subsides within 3 weeks (Table I). The injection sites can be visible as faint bluish small marks for several weeks or months but finally vanish without scarring or granuloma.

Fourteen per cent of the patients reported on blister formation at the injection sites. However, sometimes swelling of the papulae was interpreted as blisters even in the absence of any liquid contents. Therefore, all reports which described a duration of the blistering at all (186) and >2 days were regarded as plausible. So the blistering rate might be overestimated here and possibly was not >6% (160/2587). The following analyses comprise these plausible cases so that the influence of other factors on blister formation can be brought out more clearly.

Systemic symptoms

Of the 2587 treated women, 209 (8%) reported on various systemic complaints which in 143 cases (5.5%) were non-specific (Table II). In 2003, 15 women were treated for an
Adverse effects of lymphocyte immunotherapy

upper airways infection shortly after LIT which might explain their general symptoms.

Several specific complaints (Table II) were possibly coincidental (e.g. labial herpes simplex infection is not acquired haematogenously) whereas rashes reported by 14 patients are discussed regarding a suspected graft versus host disease (GvHD). One patient noted pretibial ‘dots’. This could have reflected post-transfusion thrombocytopenia (PTP) although it is not known whether she was thrombocytopenic at that time.

Antibodies to thrombocyte antigens (HPA) of the partner could not be shown 4 weeks and 8 months after LIT.

In summary, non-specific and some specific symptoms were possibly elicited by LIT in 6% (153/2587 treatments), less likely or coincidental in another 2% (56/2587 treatments). In 20 years of practising i.d. LIT, anaphylactic reactions have never occurred in our department.

Table I. Local reactions following lymphocyte immunotherapy

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Questionnaires returned</th>
<th>Proportion of complaints (n/2587) (%)</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>2371</td>
<td>92</td>
<td>15.0 ± 6.9</td>
</tr>
<tr>
<td>Itching</td>
<td>2362</td>
<td>91</td>
<td>8.4 ± 4.1</td>
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<tr>
<td>Swelling</td>
<td>1697</td>
<td>66</td>
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<tr>
<td>Burning sensation</td>
<td>779</td>
<td>30</td>
<td>5.1 ± 3.6</td>
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<tr>
<td>Blisters at injection site(^a)</td>
<td>360</td>
<td>14</td>
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<tr>
<td>Axillary lymphadenopathy</td>
<td>200</td>
<td>8</td>
<td>6.8 ± 4.3</td>
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<tr>
<td>Discomfort or pain in immunized arm, swelling of the hand</td>
<td>41</td>
<td>1.6</td>
<td>From hours up to 1 week</td>
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<td>Haematoma at injection site</td>
<td>2</td>
<td>&lt; 0.1</td>
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\(^a\)Overall number of treatments 3246, feedback 2587 (83%) 4 weeks later.

\(^b\)For 26 women blisters were apparent for only 1–2 days, and 174/360 women did not comment on the duration. Since blister formation is a remarkable sign it may have been significant in no more than 160/2587 women (6%).

Table II. Systemic symptoms following lymphocyte immunotherapy (LIT) in 2587 treatments

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Influence of LIT variables on local or systemic side-effects

Side-effects were reported significantly more often after the first LIT than after a following one [systemic symptoms possibly caused by LIT 6.3 versus 3.3% (P < 0.05), blistering 7.3 versus 1.9% (P < 0.00001), data not shown in detail]. The number of injected lymphocytes influenced the rate of side-effects after the first LIT. In our regimen (up to 150 m lymphocytes), it was elevated by 30% when the number of injected cells doubled (Table III).

Do local blistering and rashes resemble GvHD?

Local blisters

We studied the HLA class I mismatch rate between the male donor and female host who underwent LIT for the first time. When a single HLA antigen was detected in one locus (A or B) the person was defined to be homozygous for this antigen. Homozygosity represented just one HLA match or mismatch for the corresponding partner. The evaluation included all primarily infertile women (1616/1990, 81%) or women with first trimester abortions before gestational week 11 (374/1990, 19%). Up to the 10th gestational week the rate of detectable lymphocytotoxic antibodies against paternally derived fetal HLA antigens is ≤5% (Regan et al., 1991). Thus maternal presensitization against paternal HLA antigens in this subgroup who were tested negative before treatment was presumably very low.

A detailed evaluation (Figure 1) shows that the mismatch rate of the group who noticed blisters did not differ from those without blisters. High mismatch rates did not predispose to blister formation. This was apparent in the whole groups who did or did not complain of blisters (data not shown) as well as in the subgroups who received ≥40 × 10⁶ lymphocytes.
Rashes

After 2587 LIT cycles 14 patients reported on rashes. Four of 14 cases were obviously coincidental: facial allergic rash, local reaction after LIT, exacerbation of facial acne, cercarial dermatitis (‘swimmer’s itch’). Ten patients described itching rashes of differing duration (2 days to 12 months) and location. Two women complained of other symptoms which in one case strongly suggested viral upper airway infections. Four patients did not feel the need to consult their local doctor, the others were diagnosed to have light-induced dermatitis, atopic dermatitis, and chronic urticaria. Eight patients complained after their first LIT. Two had rashes after the second LIT, the first being uneventful. Liver enzymes before and 4 weeks after LIT were normal in all 10 patients. The GvH class I mismatch rate was 3.0 (range 1–4) and thus did not differ from the general mismatch rate (see Table IV). Therefore these cases did not reveal evidence for systemic GvHD.

Incidence of autoimmune diseases after LIT

From 1996 to 2002, 3042 IVF couples were treated by LIT; 1914 of them (63%) responded to the questionnaire 2–3 years after the first treatment. Eight of these (0.4%) suffered from suspected autoimmune disease (Table V). The incidence of confirmed autoimmune disease was 0.1% per year.

Discussion

Comparison with vaccinations for infectious diseases

Side-effects of allogeneic LIT can be compared with those observed after vaccination for infectious diseases since both are applied to healthy immunocompetent individuals. Some inactivated viral vaccines can also be administered intradermally. Rabies, influenza and hepatitis B vaccines applied i.d. were shown to be nearly as effective at 10–20% of the dose recommended for i.m./s.c. application (Lau and Sisson, 2002; Kenney et al., 2004). Therefore, the i.d. route is regarded as more immunogenic. However, the i.m. or s.c. applications are generally preferred because they are quicker and lead to less...
intense local reactions. Up to 30% of the vaccinees develop a local reaction to i.m. or s.c. vaccination (Centers for Disease Control, 1996), whereas after i.d. inoculation 31–85% are affected (Rivey et al., 1991; Lau and Sisson, 2002). Redness, itching, and induration of the papules are observed which subside with a bluish tinge over weeks or months. They are not caused by the adjuvant, nor are they accompanied by granuloma or scarring (Clarke et al., 1989). Systemic effects occur in ≥2–10% of vaccinees after i.m. or s.c. administration of inactivated vaccine. They can consist of low grade fever for 2 days, headache, malaise, limb pain, lymphadenopathy, and gastrointestinal symptoms and are explained by immune complex formation or cytokine release (Centers for Disease Control, 1996).

After LIT, local reactions are somewhat more intense than after i.d. vaccination for infectious diseases. Blistering is a specific feature of LIT. According to the short-term questionnaires, systemic reactions are also similar to those reported after vaccination. Cooling, local antihistamine jellies or non-steroidal anti-inflammatory drugs were prescribed where necessary. Moreover, as discussed below, 8/1914 patients suffered from suspected newly developed autoimmune disease within 2–3 years after LIT according to the long-term questionnaires.

Persons who develop urticaria and rashes tend to be alarmed, but often the symptoms are transient and the aetiology remains unclear. The 1991–2001 Vaccine Adverse Event Reporting System (VAERS report) consists of all complaints passively registered by the Centers for Disease Control and the US Food and Drug Administration. Cutaneous symptoms were reported after 11 of 100,000 vaccine doses. They comprise 43% of all complaints as well as fever (Zhou et al., 2003).

In contrast to the VAERS register, our patients were interviewed prospectively. Fever was the most common systemic complaint (81/2587, 3.1%), whereas exanthema was a rare event (14/2587, 0.5%). Infection due to LIT apparently did not contribute. We cannot exclude that LIT might cause cutaneous symptoms. Nevertheless, other causes such as allergic reactions, viral infection or cercurial dermatitis can be relevant differential diagnoses. After the first LIT, our patients reported significantly more often on local adverse effects than after any following one. This result might have been influenced by the fact that patients became used to the procedure and observed the reactions less accurately.

**Microchimerism, GvHD and autoimmunity**

**Microchimerism**

Isolated allogeneic graft cells can persist in their host in a stable asymptomatic equilibrium over years. As in solid organ transplantation and in pregnancy, microchimerism was thought to be an important factor of immunomodulation after LIT. At present knowledge, though, it does not reflect immunological tolerance towards the graft tissue (Adams and Nelson, 2004).

One study group detected DNA fragments of HLA-DR alleles which were donor specific in blood specimens of eight women who had undergone LIT for recurrent miscarriage (Prigoshin et al., 1999). However, they did not examine whether viable donor cells were actually present in the blood specimens.

Long-lasting microchimerism, e.g. after pregnancy, might be a link to development of systemic autoimmune disease such as scleroderma (Nelson, 2001). So the application of mononuclear cells has raised concern as to whether autoimmunity can be induced. However, a link from transfusion of cellular blood products to autoimmunity has not been described.

Unlike microchimerism, GvHD can be caused by allogeneic viable T-cells which gain access to the circulation and are able to proliferate. GvHD affects hosts whose immune system is compromised (Hentschel et al., 1995).

Clinical aspects of GvHD are illustrated in order to facilitate the discussion on the symptoms observed after LIT. After stem cell transplantation, an acute GvHD occurring within the first 100 days is distinguished from a chronic GvHD which

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**Table V. Autoimmune disease and deep vein thrombosis (DVT) after lymphocyte immunotherapy (LIT)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Diagnosis</th>
<th>External laboratory investigation for coagulation abnormalities</th>
<th>Time interval from LIT until clinical diagnosis</th>
<th>Outcome of IVF treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiple sclerosis, 2nd episode</td>
<td>Not performed</td>
<td>6 months</td>
<td>Abandoned</td>
</tr>
<tr>
<td>2</td>
<td>Grave’s disease</td>
<td>Not performed</td>
<td>First episode 12 years ago</td>
<td>Abandoned</td>
</tr>
<tr>
<td>3</td>
<td>Glomerulonephritis (unspecified)</td>
<td>No records available</td>
<td>1.5 years</td>
<td>Abandoned</td>
</tr>
<tr>
<td>4</td>
<td>Complex autoimmune disorder (Hashimoto thyroiditis, gastritis, joint pain)</td>
<td>No records available</td>
<td>1.5 years (gastritis 1 year before LIT)</td>
<td>Pre-eclampsia, childbirth</td>
</tr>
<tr>
<td>5</td>
<td>DVT both lower legs (2nd trimester of pregnancy)</td>
<td>In pregnancy no hereditary coagulation defects or APS detected</td>
<td>2 years</td>
<td>Caesarean section at term, singleton</td>
</tr>
<tr>
<td>6</td>
<td>DVT right axillary vein (6th gestational week)</td>
<td>No records available</td>
<td>1 year</td>
<td>Twins born at term</td>
</tr>
<tr>
<td>7</td>
<td>DVT left external v. jugularis (7th gestational week)</td>
<td>Post partum no abnormalities detected</td>
<td>4 months</td>
<td>Twins born preterm</td>
</tr>
<tr>
<td>8</td>
<td>DVT right lower leg (post partum)</td>
<td>3rd event in 14 years, treated for hyperhomocysteinaemia, no other hereditary coagulation defects or APS detected</td>
<td>1 year</td>
<td>Caesarean section at term, singleton</td>
</tr>
</tbody>
</table>

All patients were referred for IVF implantation failure. Retrospective testing for cardiolipin and phospholipid antibodies before and 4 weeks after LIT revealed normal values in all cases with DVT (data not shown).

APS = antiphospholipid syndrome.
becomes manifest later (Karrer et al., 2001). Acute GvHD affects ∼50% of patients and in the initial stage does not impair the long-term outcome. It leads to cholestasis, gastrointestinal and cutaneous acral symptoms. A maculopapulous rash can develop on face, limbs, and in the axillary regions. Chronic GvHD is a severe multi-organ affection and leads to pigmentary disturbances of the skin. A high grade of HLA discordance between graft and host basically increases the likelihood of GvHD. Transfusion-induced GvHD is an entity which very rarely can affect hosts with a supposedly intact immune system. The HLA mismatch rate is reported to be low. Patients who receive a transfusion from a first-grade relative, HLA class I-compatible thrombocytes, or donor-specific transfusion preceding solid organ transplantation, are at risk, as are elderly patients or patients undergoing multiple transfusions. The transfusion-associated GvHD progresses rapidly and is also directed against the haematopoetic cells of the host. Approximately 10 days—sometimes only 4 days—after the transfusion a maculopapulous rash associated with fever and gastrointestinal symptoms spreads from the trunk to the limbs. Uncontrollable bleeding and infections lead to death in ∼90% of cases (van der Mast et al., 2003). In blood banking, ionizing radiation of blood products is a generally accepted method to reduce the risk of GvHD. Therefore, it is recommended for the groups at risk according to the international guidelines (Combs et al., 2002).

Assessment of our data on acute adverse effects

Blister formation at the injection sites after i.d. LIT has been published in one case report (Katz et al., 1992) and was interpreted as a form of local GvHD. In our experience blisters occur in ∼6–14% of the patients, preferentially after the first LIT. If blistering were a local symptom of a GvH reaction there should be a higher HLA mismatch rate between the male donor and the female host than in cases without blisters. The effect should be more evident when larger numbers of lymphocytes are applied. Scarring, depigmentation, or general malaise would have to be expected. All these signs were not reported nor were they observed by us in any patient. Moreover, blistering is independent of the number of HLA class I mismatches. We have not investigated HLA class II mismatches but expect similar results due to linkage disequilibrium of HLA class II and I genes. Therefore, we conclude that blisters do not represent a ‘local GvH’ reaction. Most likely blistering after i.d. LIT reflects the immune response of the host (‘host versus graft’) in a cellular milieu which has been damaged by intradermal inoculation. It might be triggered by activated allogeneic cells which for example release cytokines.

Exanthema can rarely occur following LIT. As discussed above, differential diagnoses have to be considered, and some cases may purely be coincidental.

As the skin is an organ of immune defence it contains remarkable numbers of dendritic cells [roughly 10⁷μl (McLellan et al., 1998)] which are the most effective antigen-presenting cells to elicit a primary T-cell response. In blood their concentration is lower (0.1% of leukocytes, i.e. 10⁴μl). In contrast to i.v. injection, i.d. as well as i.m. or s.c. application provides a depot with a high antigen density. These factors may play a role in eliciting a good immune response with i.d. application of vaccines and might also be valid for LIT. Couples undergoing infertility treatment do not usually belong to one of the risk groups mentioned above for developing GvHD, with the exception of consanguineous couples. Therefore, we do not consider irradiation of the lymphocyte suspension, but as a precaution we conduct HLA class I typing and preclude HLA-identical couples from treatment.

Autoimmune disease

Nearly 0.1% of the European and North American population per year develop some autoimmune disease. Overall prevalence is reported to be 5%, and females are more often affected than males. Therefore, an incidence of ≥0.1% per year should be expected for women who are treated for infertility (Jacobson et al., 1997; Cooper and Stroehla, 2003).

Autoimmunity and LIT in the literature

A retrospective meta-analysis indicated that the prognosis of women with recurrent miscarriage who suffer from a systemic autoimmune disease cannot be improved by LIT (Recurrent Miscarriage Immunotherapy Trialists Group, 1994). Another aspect was the possibility that LIT might induce autoimmune disease. This assumption was refuted concerning the antiphospholipid syndrome (Moncayo et al., 1990; Christiansen et al., 1992; Doherty et al., 1992; Kilpatrick, 1992). The above mentioned meta-analysis showed that the incidence of autoimmune disease following LIT (3/1149) did not exceed that of the control group (1/410). One case of autoimmune hepatitis in pregnancy after LIT was presumably published a second time since the author contributed to the meta-analysis (Poulsen et al., 1994).

Assessment of our data concerning autoimmunity following LIT

Within 2–3 years after LIT, four of 1914 patients had an autoimmune disease diagnosed (annual incidence 0.1%). Moreover, thromboembolism can be a symptom of an antiphospholipid syndrome. Maternal thromboembolism accounts for perinatal morbidity with a frequency of 1:1000 pregnancies. Hereditary thrombophilia, administration of steroid hormones, multiple gestation, operative delivery, and pre-eclampsia contribute to the complication rate. Thus pregnancies achieved after assisted reproductive treatment are especially at risk (Lindqvist et al., 1999). The haemostasiological investigation of the four patients of our group unfortunately was incomplete, but none had developed cardiolipin or phospholipid antibodies after LIT. So an antiphospholipid syndrome leading to thromboembolism was unlikely. If these four patients were included for the sake of completeness the annual incidence of autoimmune disease would reach 0.2% and thus would correspond to the incidence expected in the female population. It should be taken into account that little more than half of the patients (63%) answered the questionnaire but we assume that women who developed some sort of disease felt more urge to report on it. So we cannot exclude that the incidence of autoimmune disorders is underestimated in our study, but to date we do not find any evidence that LIT might trigger autoimmune disease.

In conclusion, the pro- and retrospective evaluation on a large number of treatments provided by a single centre shows that the acute side-effects of intradermal LIT are of very limited
severity in immunocompetent women of childbearing age. They mainly resemble those reported after intradermal vaccination for infectious diseases. There is no evidence that anaphylaxis, graft versus host reaction or autoimmunity are elicited by intradermal LIT. Thus some serious concerns about LIT can be put into perspective.

Transfusion-related side-effects have to be taken into account as well. In our experience, they are also low, so that the further use of this treatment is justified. Residual risks can be minimized by certain diagnostic measures and selection criteria. In the context discussed here, consanguinity and HLA class I typing should be considered.

References


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