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Post-transplant Lymphoproliferative Disorders after Solid Organ Transplantation in Children

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Rezumat

Bolile limfoproliferative secundare transplantului de organe solide la copii

Boala limfoproliferativă post-transplant (PTLD), raportată pentru prima oara în 1968, este o complicație întâlnită atât în transplantul de organe solide (SOT) cât și în transplantul de măduvă osoasă (BMT) și este asociată cu utilizarea imunosupresiei terapeutice (IS). Factorii de risc, tratamentul şi evoluția bolii diferă între PTLD observată în BMT şi SOT. PTLD este o complicație potențial fatală în evoluția clinică a pacienților transplantați şi reprezintă cea mai frecventă complicație malignă după SOT la copii, și a 2-a ca frecvență la adult. (1,2) Acest articol prezintă factorii de risc care predispun la dezvoltarea PTLD, aspectele clinice, de diagnostic şi opțiunile terapeutice în PTLD, cu scopul de a obține o remisiune completă durabilă cu toxicitate minimă. Diversitatea formelor clinice, uneori cu evoluție rapidă agresiv, împreună cu heterogenitatea aspectelor imagistice şi histologice, accentuează importanța unui grad crescut de suspiciune clinică la această categorie de pacienți, care să permită diagnosticul precoce şi tratamentul adecvat cu efect favorabil asupra rezultatelor.

Cuvinte cheie: boala limfoproliferativă posttransplant (PTLD), virus Ebstein-Barr (EBV), transplant de organe solide (SOT), copii

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Abstract

Post-transplant lymphoproliferative disease (PTLD) is a well recognized complication of solid organ transplantation (SOT) or bone marrow transplantation (BMT) associated with therapeutic immunosuppression (IS), first reported in 1968. Risk factors, therapy, and outcomes differ between PTLD observed following BMT and SOT. PTLD is a potentially fatal complication in the clinical course of transplant recipients, representing the most common malignancy after SOT in children and the second in the adult setting. (1,2) This review presents the predisposing risk factors to the development of PTLD, along with clinical aspects, diagnostic work-up and therapeutic options in order to obtain a durable and complete remission with minimal toxicity. The extreme diversity of clinical presentations, sometimes with rapidly aggressive evolution, together with the heterogeneity of imagistic and histological findings, have proven the importance of the high degree of clinical suspicion. The early recognition and the prompt adequate treatment may improve the outcome.

Key words: posttransplant lymphoproliferative disease (PTLD), Ebstein Barr virus (EBV), solid organ transplantation (SOT), children

Introduction

Post-transplant lymphoproliferative disorder represents a life threatening complication in solid organ transplant recipients. It constitutes a heterogeneous group of diseases, often associated with Epstein–Barr virus (EBV) infection and long-term immunosuppression. The risks of developing cancer

after receiving a transplant is increased up to about 5-10 times as compared to the general population; children, especially those younger than 10 years old, have more than 50-fold increased risk over the general pediatric population. (3,4) Post-transplant malignancies do not mirror the types of cancer seen in the nontransplant pediatric population, but they are quite similar to what it is observed in other immunodeficient populations. PTLD is more common in pediatric age due to children's EBV seronegative status before transplant, high prevalence of seropositivity among donors, and frequent development of infection within the first year after transplantation. Different studies conducted on relatively small populations of children have shown an incidence with a varying range of 1% to 30%. (5) Less than 20-30% of PTLD following SOT in children are not EBV-positive. (6) EBV lymphoproliferative post-transplant disease may manifest as isolated hepatitis, lymphoid interstitial pneumonitis, meningo-encephalitis, or an infectious mononucleosis-like syndrome. Less frequently, PTLD may present as rapidly progressive, disseminated disease with multiorgan system failure. Despite its rarity, when it occurs PTLD presents with a high mortality rate. Clinical presentations are extremely protean and consequently a high index of suspicion is essential for an early diagnosis. The first line treatment of all PTLD is immunosuppression reduction (RIS). The surgical resection and or radiotherapy should be considered for localized disease. For advanced/progressive disease different strategies combining RIS, antibody therapy, chemotherapy are recommended.

Risk factors

a. EBV status at the time of transplantation

EBV is a latent γ-herpesvirus that infects more than 90% of the world's population. Primary infection occurs usually in early childhood and is asymptomatic or it may present later as infectious mononucleosis. In immunocompetent hosts, the primary infection is resolved by cytotoxic T-cell-mediated immunity, but the host carries silently a low number of EBV episomes in the resting memory-B-cell compartment for life, establishing latent infection characterized by the expression of only a limited array of subdominant EBV antigens. There are 4 types of latency, presented in *Table 1*, distinguished by the pattern of EBV antigen expression in infected memory B cells.

Transplant recipients, undergoing prolonged immuno-suppressive therapy to prevent allograft rejection, present impaired immune surveillance, with low virus-specific CTL (cytotoxic T lymphocyte) reactivity and are susceptible to chronic EBV active infection. (8,9) The primary risk for PTLD after SOT appears to be seronegativity at the time of transplant. (10) EBV seronegative status correlates with a 4.7 to 30-fold higher risk to develop PTLD, compared to EBV positive subjects and these odds are increased by EBV donor+/recipient– (D+/R–) cases, when children may experience primary infection very soon post-transplantation. The median reported interval ranges from 3 months to one year. (11,12,13)

Even though many studies have already provided important data, the precise mechanisms by which EBV infection induces lymphocyte proliferation are still unknown. EBNA-1 is expressed in all EBV-carrying malignancies and it seems to contribute to oncogenesis by causing chromosomal aberrations, DNA double-strand breaks, and commitment of the DNA damage response. This genomic instability is further associated with high production of reactive oxygen species (ROS). (14) A study conducted by Maria-Rosa Ghigna et al in 2009 has focused on three families of molecules that play major roles in apoptosis control of immune cells and seem implicated in tumor development: anti-apoptotic members (including Bcl-2, Bcl-XL and Mcl-1), pro-apoptotic proteins (Bax and Bak) and the so-called BH3-only proteins (Puma, Bad, Bid and Bim). Immunohistochemistry examinations carried out on 62 PTLD cases shown that the first two groups do not display any correlation with EBV infection in PTLD, whereas Bim is the only member of the BH3-only proteins significantly related. Bim pro-apoptotic action after binding to pro-survival Bcl-2 proteins, together with much lower expression in EBV+ PTLDs, suggests that it might be targeted by different EBV latent proteins, with subsequent induction of aberrant proliferation. (15)

b. Immunosuppressive agents

The major modifiable risk factor for PTLD in SOT is the degree of immunosuppression. However, there is no consensus as to whether any one particular IS agent is particularly responsible or even the overall degree of immunosuppression is directly linked to an increased risk of PTLD. Many studies conducted during the last three decades have pointed out most IS agents to be an important factor in PTLD pathogenesis: calcineurin inhibitors (cyclosporine A and tacrolimus), mammalian target of rapamycin (mTOR) inhibitors or proliferation signal inhibitors (PSIs) such as sirolimus and everolimus, anti-CD3 monoclonal antibody (OKT3),

Table 1. *EBV latency types (adapted from Heslop H, Blood 2009) (7)*

Latency type	Type 3	Type 2	Type 0	Type 1
Viral proteins	EBNAs: 1, 2, 3a, 3B, 3C, LP, LMP1,2	EBNA1, LMP1,2		EBNA 1
Normal B cell	Naive B	Germinal center B	Resting memory B	Dividing memory B
Malignant counterpart	PTLD	Hodgkin lymphoma, nasopharingeal carcinoma		Burkitt lymphoma, gastric carcinoma

Legend: EBNA= EBV nuclear antigen, LMP= latent membrane protein

polyclonal T cell depleting antibodies (anti-lymphocyte globulin ALG and anti-thymocyte globulin ATG) and antimetabolites (mycophenolate mofetil MMF or azathioprine). However, the overall results in different studies are still controversial and there is no consensus as to whether any single immunosuppressive agent is particularly responsible for PTLD. Even more, the BCSH and BTS Guidelines in 2010 advise not to choose a certain immunosuppressant regimen over another because of a potential PTLD risk (Grade B, Level 3 of evidence). (16) Along with this opinion, most studies do agree that it is the intensity of IS to have a more important impact, while raising awareness of the difficulties they encounter to quantify it: drug combination in most protocols, poor registration of exact dose evolution and repeated anti-rejection case-dependent therapies. (16,17) In particular, two or more acute rejection episodes in the first 3 months after transplantation have been pinpointed as additional risk factor. (18) An example of heavy immuno-suppression and its costs has been alerted by R. A. McDonalda et al in 2008. A "robust" regimen including basiliximab, calcineurin inhibitor, sirolimus and steroids was administered to 274 pediatric renal recipients in order to prevent early acute rejection. PTLD incidence among them was much higher than previous reported rates: 6.9% in comparison with 1.2-4%. Even though the protocol partially achieved the aim and a lower rejection rate was registered, the number of PTLD cases and infectious complications urged the authors to discourage its use. (19) In contrast, minimalistic post-kidney transplant monotherapy with close follow-up in order to avoid graft loss seems safe and effective, with no PTLD incidence, irrespective of the IS agent in use (ATG, alemtuzumab, tacrolimus or sirolimus). (20)

c. Age and transplant type

PTLD is more common in children under 10 years old and adults over 69 years old when compared with the normal population. The increased incidence in children is seen within the first 3 months post-transplantation and it is primarily thought to be due to primary EBV infection. (21,22) The type of transplant has also been identified as a risk factor. (*Table 2*)

Clinical features

The clinical features of PTLD are often non-specific. There are 2 peaks in the incidence of PTLD: in the first 12 months after transplant (early PTLD) and 5-10 years after transplant (late PTLD). The primary EBV infection manifested in children after transplant is identical with systemic mononucleosis, with fever and lymphadenopathies especially in the cervical nodes and Waldayer's ring. (24)

Frequently, the definition of PTLD is limited to lymphomatous lesions (localized or diffuse) that are often extranodal, commonly in the transplanted organ (15-20% of patients). (25) In heart, lung and liver transplant setting, the PTLD occurs in the 52% of cases in the transplanted organ, whereas in kidney transplant recipients, the commonest sites were gastrointestinal and central nervous system. (26)

The classical presentation of enlarged lymph nodes seen in adult non-transplant population is relatively uncommon, irrespective of the transplant type, with extranodal involvement being seen most commonly. The presenting features are more often caused by the interference with the function of the involved organ. The classic B symptoms of weight loss, sweats, and pyrexia still occur. Most patients with PTLD are diagnosed in an advanced stage (III-IV).

Table 2. *PTLD frequency by age and transplanted organ (Opeltz & Dohner, 2004) (23)*

Organ	Adults (%)	Children (%)
Kidney	1 -2,3	1,2-10,1
Liver	1 -2,8	4-15
Heart	1 -6,3	6,4-19,5
Heart/lung	2,4-5,8	6,4-19,5
Lung	4,2-10	6,4-19,5
Small bowel	20	30

Diagnostic work-up

a. Tissue biopsy and histopathological classification

The diagnosis of PTLD should be based on histological examination of tumor tissue obtained by surgical excision biopsy or needle core biopsy. In some cases the sole site of involvement may be bone marrow (BM) or CNS.

The pathological diagnosis of PTLD is based on WHO 2008 classification. There are four major WHO categories of PTLD: early lesions, polymorphic PTLD, monomorphyc PTLD and classical Hodgkin-lymphoma-type PTLD. The pathological investigative techniques in PTLD recommended are summarized in *Table 3*.

The presence of infiltrating T cells, the disruption of nodal architecture and necrosis are the major features in distinguishing polymorphic PTLD from early lesions. Histological patterns observed in the monomorphic subtype are similar to the de novo non-Hodgkin lymphoma (NHL), with diffuse large B-cell lymphoma (DLBCL). These are the most common histological findings, and they are less frequent as compared to less frequently Burkitt or Burkitt-like lymphoma. This is in contrast to what it is observed in NHL in children outside transplant setting, where Burkitt or lymphoblastic histologies predominate. (28) A rare monomorphous B-cell subtype of PTLD is multiple myeloma or plasmacytoma. In PLTD, as opposed to de novo NHL, there appears to be no difference in histologies between pediatric and adult cases. (29) (*Table 4)*

PTLDs of T-cell or natural killer (NK)-cell origin constitute an uncommon heterogeneous group of typically EBV–, extranodal lymphomas. They often occur much later than many other PTLD (a median of 66 months), particularly compared with EBV+, usually do not respond to a simple decrease in immunosuppression, and have an adverse prognosis, with a median survival of 6 months. The most common types reported are peripheral T-cell lymphoma,

Table 3. *Pathological investigative techniques in PTLD (after Harris et al 2001) (27)*

Technique	Necessity	Purpose
Morphology	Essential	Architecture (preserved/effaced) Cytology (polymorphic/monomorphyc) Identification of specific morphological features
Immunophenotyping	Essential	Lineage Light chain restriction (flowcytometry or immunohistochemistry) Prognostic factors in some lymphomas
EBER ISH	Essential	Detection of EBV
Molecular genetic studies of antigen receptor genes	Useful	Clonality
FISH	Rarely required	Detection of specific translocations in some lymphomas
EBV clonality	Rarely required	Identification of minor clones

Legend: EBER ISH= EBV-encoded RNA (EBER) in situ hybridization

Table 4. *PTLD – Summary of biological characteristics (after Parker et al, 2010) (16)*

PTLD category/incidence	Histology	Immunophenotype	Molecular analysis
Early lesions (5%) Plasmacytic hyperplasia (PH) Infectious mononucleosis-like (IM-like)	Preservation of underlying tissue architecture. PH exhibits plasma cells with scattered immunoblasts. IM-like lesions show predominantly immunoblasts, sometimes with RS like cells and/or plasmacytic differentiation.	Plasma cells show polytypic light chain staining. Immunoblasts are CD20+, CD79a+, PAX-5+, CD30+, CD15-. Admixed T-immunoblasts present (CD3+, CD5+). EBER positivity in B-immunoblasts.	Oligoclonal or polyclonal IgH and T-cell receptor (TCR) genome. EBV genome oligoclonal or polyclonal.
Polymorphic PTLD (15-20%)	Effacement of underlying tissue architecture and a mixed infiltrate with small lymphocytes, intermediate-sized lymphocytes, immunoblasts and plasma cells. There may be necrosis, a high mitotic rate and nuclear atypia.	B cell (CD20, CD79a, PAX-5) markers are positive and CD138 highlights plasma cells. The majority of B cells are EBER+. Light chains may be polytypic or monotypic.	Clonal IGH genome (TCR is usually polyclonal). Clonal EBV genome.
Monomorphic B-cell PTLD (>70%) Diffuse large B-cell lymphoma (DLBCL) Burkitt lymphoma (BL) Plasma cell myeloma Plasmacytoma-like lesion Other	Destruction of underlying tissue architecture and malignant cytological features. **DLBCL type** presents immunoblastic, centroblastic or pleomorphic morphology. **BL type** shows monomorphic cells with prominent apoptosis ('starry sky' pattern). Plasmacytic lesions contain sheets of mature plasma cells.	**DLBCL B-PTLD** is CD20+, CD79a+, and PAX-5+. May be focally CD30+. Light chain restriction in 50%. EBER+. **BL-PTLD** is CD20+, CD10+, BCL2) with approaching 100% positivity using Ki67/MIB1. EBER+. Light chain restriction is common. **Plasma cell myeloma and plasmacytoma-like PTLD** is CD138+, VS38c+, CD20) (usually), CD79a+. Light chains are monotypic. EBER±	Clonal IGH genome (TCR usually polyclonal). Clonal EBV genome if EBVpositive. **BL-PTLD** displays MYC rearrangement.
Monomorphic T-cell PTLD (<5%) Peripheral T-cell lymphoma, not otherwise specified Hepato-splenic lymphoma Other	Destruction of underlying tissue architecture and malignant cytology. A wide range of morphological appearances depending upon the type of T-cell lymphoma.	Variable expression of pan-T antigens (CD3, CD5, CD2, CD7). Any combination of subset markers. Cytotoxic markers often positive. CD30 can be positive and aberrant CD20 expression can be seen. T/NK cases are CD56+, CD3-. Most (60–90%) T-cell cases are EBER-. T/NK cell lesions are usually EBER+.	Clonal TCR genome (germline in T/NK lesions). IgH can be polyclonal or monoclonal. EBV genome clonal (if present).
Classical Hodgkin lymphoma–like PTLD (<5%)	RS cells and/or Hodgkin cells on the typical CHL background.	HL-PTLD shows classical phenotype – CD30+, CD15+, CD45), CD20), CD3). RS cells usually EBER+.	IGH genome can be monoclonal or polyclonal (TCR usually polyclonal). EBV genome is clonal.

RS cells = Reed Sternberg cells

unspecified, and hepatosplenic T-cell lymphoma, whereas the rarest are primary cutaneous anaplastic large cell and extranodal NK/T-cell lymphoma, nasal type lymphomas. Nevertheless, exceptions to each of these generalizations have been described. Some T/NK-cell PTLDs occur shortly after transplantation, almost a third are EBV+, rare cases have achieved CR without chemotherapy or radiation, and some patients have a prolonged survival. Most cases have been reported among renal transplant recipients. (16)

b. Pre-treatment assessment and staging

All patients with PTLD require a comprehensive

pre-treatment evaluation in order to assess the function of the transplanted organ and the PTLD extension. The baseline blood tests should include full blood count, electrolytes, glucose, liver enzymes, urate, lactic dehydrogenase, and virology (HIV, hepatitis B, C). In pediatric age, abdominal ultrasonography remains the first-line screening technique recommended for detection of intraabdominal masses. (30)

CT scan of the chest, abdomen and pelvis has been described as essential for an accurate staging (4,31) while fluorodeoxyglucose-positron emission tomography (FDG-PET) has proven an increased sensitivity in comparison with conventional methods of PTLD visualization. (32) It appears extremely useful in kidney recipients with compromised renal function when i.v. contrast should be avoided. (5) Moreover, PET/CT provides valuable additional data for therapeutic management. However, the findings of both PET and PET/CT should be interpreted in close relation with the histological-analysis, since false positive results have been reported. (33) Magnetic resonance imaging (MRI) is extremely helpful in the diagnosis of bone and CNS involvement. A bone marrow aspirate and biopsy should be performed in any patient with abnormal peripheral blood counts; for patients with suspected CNS disease a lumbar puncture followed by immunophenotyping by flow cytometry and cytology analysis is mandatory for the diagnosis as well as for the staging. The patients should be staged using Ann-Arbor staging system, however with limited application in PTLD due to the high predisposition for extranodal involvement. (34)

Therapeutic options

Historically, the treatment options, which were not standardized, included: reduction of immunosuppression (RIS), interferon-alpha, or other antiviral, anti B-cell antibody (rituximab), various chemotherapy regimens, surgery, and radiotherapy. Usually these treatment strategies are employed sequentially, starting with RIS and progressively escalating to chemotherapy, if the response to prior strategies was inadequate. However, it is not clear whether a sequential approach provided a better outcome.

a. Restoring the immune response to EBV - Reduction of immunosuppression (RIS)

As soon as the PTLD diagnosis is suspected, immediate reduction in immunosuppression (RIS) should be considered. Because RIS carries out the risk of graft rejection, the graft function must be monitored closely, especially in the heart, lung and liver allograft recipients, for whom no effective alternatives are available if rejection occurs. Ideally, RIS should be done over several months, but this is not always possible, particularly in aggressive disease. (35) Factors predicting the failure of RIS as single treatment modality include monomorphic histology, elevated LDH, organ dysfunction, and multiorgan involvement. The strategy of RIS monotherapy is reasonable in SOT recipients with limited disease, but should be considered as part of a complex treatment management in all patients with PTLD.

b. Targeting B cells – rituximab and/or chemotherapy

As most cases of PTLD arise in donor-derived B cells (in BMT recipents) and in recipient-derived B cells (in SOT recipients), one strategy for prevention and treatment is to eliminate EBV-infected B cells with antibody therapy targeting specific B-cell surface antigens present on the EBV-transformed malignant B-cells. The most widely used antibody is rituximab, a chimeric murine/human monoclonal antibody anti CD20. CD 20 expression is not confined to the malignant cells and the normal B cells are also destroyed by rituximab, representing a significant concern in patients who are already immunosuppressed, with a potential risk for fatal infections.

In two independent large, multicenter prospective phase II trials rituximab monotherapy was administered at a dose of 375 mg/m^2 weekly, for 4 courses and showed 52% complete remission (CR) in the Oertel study (36) and 28% CR with 44% overall response rate in the Choquet study (37). In conclusion, in adult patients with PTLD after SOT, rituximab monotherapy (4-8 courses) is recommended for clinical low risk PTLD who fail to respond adequately to RIS. Clinical low risk is defined as none of the following risk factors: age < 60 years, high LDH level, performance status ECOG grade 2-4.

In 2003, the European Study Groups on PTLD initiated a prospective, multicenter phase II trial to investigate the efficacy and safety of R-CHOP 21 chemotherapy (rituximab, cyclofosphamide, doxorubicin, vincristine, prednisolone) in PTLD failing to respond to RIS. The overall response rate was 89% with 69% CR (38), higher as compared to Rituximab monotherapy. Rituximab plus anthracycline based chemo-therapyn (e.g. CHOP) is recommended for patients who fail to achieve an adequate remission or progress despite RIS and rituximab monotherapy. For patients with clinically aggressive lymphoma or critical organ compromise, rituximab plus anthracycline based chemotherapy plus RIS should be considered at any time following diagnosis. (16)

In children, Gross et al. evaluated the efficacy of a low dose chemotherapy regimen (Ciclophosphamide 600 mg/m^2/day, 1 day + Prednison 2 mg/kg/day, 5 days, repeated every 3 weeks, 6 cycles) in EBV positive PTLD and reported overall response rate 73%, relapse free rate 69% and failure free rate 67% at 2 years. To note, this regimen did not work in fulminant PTLD cases in children. (32) Gupta and colleagues analyzed the efficacy of adding rituximab to the low dose chemotherapy regimen in patients after RIS failure and reported a small series of 8 patients with PLTD EBV positive and registered a 100% CR rate with low relapse rate – only 8%. (39)

c. Additional therapies - Surgery and radiotherapy

If PTLD appears to be localized, local surgical resection and/or radiotherapy can effectively control the disease, in association with RIS, but only a minority of heart, liver and kidney PTLDs are localized at presentation. (40) Surgical excision may be required for a tissue biopsy or is required for

Table 5. *Summary of current indications for PTLD treatment (Parker 2012, Zimmermann 2011) (16,25)*

PTLD category	First line therapy	Second line therapy	Alternatives
Early lesions Plasmacytic hyperplasia (PH) Infectious mononucleosis-like (IM-like)	RIS	R-chemo	
Polymorphic PTLD	RIS	R-chemo	
Monomorphic B-cell PTLD			
• Diffuse large B-cell lymphoma (DLBCL)	RIS + R-chemo	Salvage therapy – carboplatin + etoposide (adult patients)	Surgery/radiotherapy for localized disease
• Burkitt lymphoma (BL)	RIS + R-chemo		
• Plasma cell myeloma	Stage I Plasmocytoma – radiotherapy or surgery		
• Plasmacytoma-like lesion			
• Other			
Monomorphic T-cell PTLD			
• Peripheral T-cell lymphoma, not otherwise specified	RIS + chemotherapy (CHOP)		Surgery/radiotherapy for localized disease
• Hepato-splenic lymphoma			
• Other			
Classical Hodgkin lymphoma lymphoma–like PTLD	Early stages – radiotherapy Advanced stages - ABVD		

the emergency management of gastro-intestinal PTLD that presents acutely with perforation, intestinal obstruction or intractable hemorrhage. Surgery and radiation also have a role in managing other local complication of PTLD, such as compression of vital organ structures.

d. Therapy for special conditions

i. PTLD affecting the CNS

Rituximab and CHOP chemotherapy do not cross the blood brain barrier; PTLD affecting CNS should be treated with RIS followed by local radiotherapy and/or steroids. Children in good condition may be considered for protocols with high-dose methotrexate. (41,42)

ii. Hodgkin Lymphoma PTLD

Hodgkin lymphoma is often associated with EBV and responds well to standard therapy. Advanced stage Hodgkin lymphoma should be treated with ABVD chemotherapy, except of patients with cardiac dysfunction or after heart transplant; localized Hodgkin lymphoma may be successfully treated with radiotherapy alone. (43) *(Table 5)*

At present, the treatments with antiviral agents, EBV-specific cytotoxic T lymphocytes, Interferon alfa, intravenous immunoglobulin, anti IL-6 antibodies are not recommended outwith a clinical trial.

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