ingly, although lack of desferal compliance has been thought to account partly for the apparent cardioprotective effect of deferiprone, compliance was 85% in the desferal-treated group and only 4% higher in the deferiprone-treated group. With this level of desferal compliance, this is unlikely to be an adequate explanation for any differences in oucomes. The importance of an orally acting agent that is cardioprotective cannot be underestimated. Further prospective and randomized studies are now needed to confirm these initial findings. Further work should also use myocardial iron measurements, and T2* is ideally suited for this.

This now raises the possibility of tailor-made chelation strategies based on differential tissue iron distributions in different patients, where desferal is better for liver iron chelation, and deferiprone more effective in the heart. More aggressive liver iron chelation may be needed in patients who are hepatitis C positive,[17] and some patients may require a combination of agents.

The use of tailor made chelation regimes and combining the 2 agents in lower doses, may both alleviate side effects, and reduce mortality and morbidity further. It is known that iron removal increases if desferal and deferiprone are used in combination. With the possibility of further chelating agents in the near future, treatment may soon be based on a cocktail of chelating agents, tailored to an individual patient's needs, and based on a sound understanding of their respective tissue iron distribution.

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Rituximab: a new therapeutic tool for primary immune thrombocytopenic purpura?

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura, is an acquired disease of children and adults defined as isolated thrombocytopenia. In pivotal experiments (which would be totally unfeasible today), Harrington and others demonstrated that infusion of whole blood or plasma from ITP patients into normal volunteers caused thrombocytopenia.[1] Moreover, subsequent studies demonstrated the crucial role of the spleen in determining platelet loss from the circulation.[2] These data strongly suggested that anti-platelet antibodies were responsible for the disease.

Many years of research have provided additional details on the nature of the antibodies involved (directed primarily against GPIIb/IIIa and/or GPIb/IX)[2,3] but still little is understood about the primary mechanism which triggers autoantibody production and, more importantly, what is the basic pathogenetic mechanism of the disease. One wide-

ly accepted hypothesis is that autoantibodies opsonize platelets and activate complement. As a consequence, platelets should be phagocytosed via Fc or C3 receptors mainly by macrophages in different anatomical sites (mostly in the spleen). Moreover, evidence suggests that uptake of opsonized platelets by dendritic cells (DC) further amplifies the autoantibody production through presentation of novel platelet antigens to the immune system.[2]

The paper by Zaya *et al.*[4] clearly documents that the chimeric monoclonal anti-CD20 antibody rituximab shows activity for the treatment of ITP, since in a group of 20 symptomatic patients, relapsed or refractory to standard therapies, rituximab (375 mg/m^2 i.v. weekly for 4 weeks) was active in 13/20 patients, producing 9 complete and 4 partial responses, as evaluated by platelet counts. Furthermore, in one table in their report (Table 7), the authors clearly summarize the published clinical data on rituximab and ITP showing that more than one hundred patients have been thus treated, and a response achieved in about 50% of the patients.

Unfortunately, when the authors tried to relate the clinical response to several laboratory observations, as indeed also reported in previous studies, no correlation could be found with CD20 levels, B lymphocyte clearance *in vivo* (achieved in all patients), circulating immunoglobulin levels of all isotypes, gender, time from diagnosis to treatment or pharmacokinetic determinations of the drug. Thus no clear explanation for the effect of rituximab or for the lack of response in some patients could be found. Thus even carefully conducted clinical studies, such as the one reported here by Zaya *et al.*, do not add much more to our understanding of the mechanism of disease and consequently do not provide new ideas on possible strategies to be envisioned to improve therapy. The situation is made more complex by the fact that the mechanism of action of rituximab in the treatment of B-cell neoplasias is likewise still not fully resolved.[5] Rituximab is an unconjugated anti-CD20 chimeric monoclonal antibody. We know, from *in vitro* and *in vivo* data, that rituximab binds to the surface of CD20 positive B cells, thus activating the complement system as well as mediating antibody-dependent cellular cytotoxicity (ADCC) through Fc receptor binding.[6-8] A more direct role of rituximab on the proliferation or apoptosis of target cells appears very controversial at this point. Most studies however, including ours, have focused on the mechanism of clearance of neoplastic rather than normal B cells by rituximab, a point that should alway be kept in mind when considering the effect of the antibody in patients with *normal* B cells. Nonetheless, the destruction of B cells *in vivo* (caused almost certainly by complement activation perhaps accompanied by ADCC and/or phagocytosis)[9] cannot be directly responsible for the response of ITP patients to the drug for two reasons: the first is that B-cell depletion occurs in all cases irrespective of the clinical outcome; the second is that the reduction of circulating B cells does not rapidly change the circulating levels of immunoglobulins (including the autoantibodies), as demonstrated in this and previous studies. On the contrary, a rise in platelet counts is observed within a few days.[10]

A recent report has suggested that rituximab-coated B cells may bind macrophages via Fc receptors (CD64 and CD16), thus diverting these cells from platelet phagocytosis (a kind of competition between antibodies for the same effector mechanism).[10] It is indeed possible that rituximab bound to B cells competes with anti-platelets antibodies, thus causing a rapid rise in platelets counts. This competition could also include competition for complement activation and for binding of C3b-coated cells to the CR3 receptors on scavenging cells, since rituximab has been shown to be very efficacious in activating the classical pathway of complement[7] and in causing C3b deposition onto target B cells *in vivo*.[11] It is of course possible that there are other mechanisms, although alternative hypotheses cannot be easily formulated at the moment. It is interesting that a similar mechanism has been proposed for the therapeutic effect of intravenous immunoglobulin, although this issue is still controversial.[12]

In this context it is important to remember that the management of chronic refractory ITP involves minimizing therapy while maintaining a safe platelet count, taking into account the possible presence of other risk factors for bleeding, the patient's compliance to changes in life style and to treatment and the potential toxic effects of therapy. Conventional second-line treatment for patients failing standard doses of corticosteroids or requiring unacceptably high doses to maintain a safe platelet count is splenectomy; 60-70% of ITP splenectomiz00ed patients achieve durable and safe platelet counts. For the non-responders or for those in whom splenectomy would be a risk-procedure, third-line treatment can be offered, considering the severity of the disease on individual bases. It is now widely accepted that experimental treatments should be applied when the risk of life-threatening hemorrhage is present, such as in the elderly (severe central nervous system or gastrointestinal hemorrhage) and not on the basis of platelet count alone. These recommendations are not fully supported by evidence-based studies but represent the opinion of many experts. The use of rituximab, an expensive drug, whose mechanism of action in autoimmune diseases is not well known, may be indicated in very selected patients. A careful and prolonged follow-up

for possible late side-effects in splenectomized ITP patients must be conducted. Further research, including clinical trials that incorporate clinically relevant end points (the severity of bleeding), quality of life assessment and economic considerations, is needed to improve management.

The results obtained emphasize the multiple therapeutic uses of rituximab as well as the urgent need for research to extend and optimize the use of this drug in the yet little explored world of autoimmune diseases.

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Non-myeloablative conditioning before allogeneic stem cell transplantation in adult acute lymphoblastic leukemia

In adult acute lymphoblastic leukemia (ALL) complete remission (CR) rates of 80-85% and leukemia-free survival (LFS) rates of 30-40% were achieved in recent studies.[1] It seems, however, that the options for further improvement are limited. This is particularly true for the high proportion of elderly ALL patients who are not covered in most trials. Nowadays many study groups refer ALL patients with high risk or very high risk (Ph/BCR-ABL positive) to allogeneic stem cell transplantation (SCT) from sibling donors in first CR with LFS rates of 30-40% in prospective studies and high risk patients.[2] This procedure is associated with nearly equally high rates of transplant-related mortality (TRM) and relapse (RR) of around 30%. The outcome of matched unrelated (MUD) SCT is approaching these results, with a somewhat higher TRM but lower RR. Results of allogeneic SCT are probably improving further by better donor selection, supportive care, etc. The complications, such as graft-versus-host disease (GvHD), organ toxicities and infections, are nevertheless considerable and the risk increases with age, comorbidities such as fungal infections, decreasing performance status or use of mismatched (MM) transplants. Alternative SCT regimens — excluding intensified conditioning — are urgently required for these patients with a high risk of TRM.

Non-myeloablative SCT or reduced intensity conditioning regimens (NMSCT) are new approaches which deserve evaluation in ALL and may lead to an extension of indications for allogeneic SCT. In contrast to conventional SCT, which mainly relies on killing cells by high-dose chemotherapy and total body irradiation (TBI), NMSCT aims to exploit graft-versus-leukemia (GvL) effects. Immunosuppression, for example, with purine analogs, other cytostatic drugs and/or low dose TBI, is followed by the infusion of donor stem cells from siblings or MUD with adapted immunosuppression to establish host tolerance.[3]

Consequently this approach can only be effective in diseases with a relevant GvL effect. NMSCT yielded quite impressive results in indolent leukemias such as chronic myeloid leukemia but also in acute myeloid leukemia.[4] There is, however, the general opinion that GvL effects are less pronounced in ALL than in other malignancies. Nevertheless these effects are present as indicated by the lower RR in patients with acute and/or chronic GvHD,[5-7] the lower RR after MUD SCT, and the induction of remissions by withdrawal of GvHD prophylaxis or donor lymphocyte infusions (DLI) in single patients with relapsed ALL.