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Thromboprophylaxis in acute medical patients: need for an implementation strategy

In 1992, the 3rd ACCP Consensus Conference on Antithrombotic Therapy noted that in contrast to the situation for surgical patients, prevention of venous thomboembolism (VTE) had been relatively little studied in hospitalized medical patients.[1] No prophylactic recommendations were given for general medical patients except in the context of myocardial infarction and ischemic stroke.[1] In 1995, the 4th ACCP Consensus Conference introduced substantial changes in this position;[2] despite Grade A recommendations based on level I data being issued concerning the use of low doses of unfractionated heparin and low-molecular-weight heparins (LMWH) in general medical patients with clinical risk factors for VTE, particularly those with congestive heart failure and/or chest infections, only one additional trial had been published between 1992 and 1995 concerning the prevention of VTE in cancer patients undergoing chemotherapy.[3]

The recommendations were, therefore, not clearly evident. The 5th ACCP Consensus Conference, published in 1998, did not modify the VTE prophylaxis recommendations for medical patients,[4] after the publication of two additional trials on patients with acute medical illnesses.[5-6] In 1999, the Medenox trial showed the efficacy of a high-dose, prophylactic LMWH regimen in preventing venographically evaluated deep-vein thrombosis (DVT) in patients with congestive heart failure, acute respiratory failure not requiring ventilatory support, or one of the following medical conditions associated with at least one additional risk factor for VTE: acute infection without septic shock, acute rheumatic disorder, acute arthritis of the legs or acute episode of rheumatoid arthritis in the legs, or episode of inflammatory bowel disease.[7]

All these medical conditions, as well as acute myocardial infarction and acute ischemic stroke, were discussed during the 6th ACCP Consensus Conference in 2001 and were considered as grade A recommendations for VTE prophylaxis.[8]

In this context, Ageno *et al.*[9] conducted a study to evaluate the prevalence of patients with these clinical conditions requiring VTE prophylaxis, and the adherence to published clinical guidelines.

Ageno *et al.* retrospectively studied 165 patients with clinical indications for VTE prophylaxis from one teaching and one non-teaching hospital. Their data suggest that among the 112 patients without clinical contraindications to anticoagulation and without oral anticoagulant treatment prior to hospital admission (e.g. for atrial fibrillation), prophylaxis was underprescribed: even though all the 112 patients met consensus guidelines for the use of antithrombotic therapy, only 52 patients (46.4%) actually received thromboprophylactic treatment. Regarding the indications for VTE prophylaxis, patients with acute ischemic stroke or congestive heart failure were more likely to receive prophylaxis than other patients, in particular those with malignant or infectious diseases, or acute respiratory failure.

Surprisingly, this study revealed that certain intuitive dose recommendations were being applied with respect to particular populations, in the absence of specific pharmacokinetic/pharmacodynamic indications; in particular, eight patients received non-validated doses of thromboprophylactic therapy because of obesity.

Could the experimental design (retrospective study) have biased the observations? We cannnot rule out this possibility, because we can assume that the more the patient is considered to be at high risk, the more information is collected, and the better and more complete the data are. Certain questions were not asked during the clinical examination and some information is therefore missing at times. All these drawbacks should disappear in the context of a prospective study. Moreover, there

were only two centers and the observed differences between the hospitals of Varese and Angera may be attributed either to the difference between a teaching and non-teaching hospital or simply to the classical differences between any two medical departments. To confirm this result, it might be worthwhile to address this question by including several teaching and non-teaching hospitals.

How can the underuse of thromboprophylaxis be explained? Two main explanations can be discussed.

First, the clinical relevance of the guidelines might not be sufficiently convincing. One could debate the clinical relevance of the 15% venographic DVT risk in acute medical patients, even though one meta-analysis has shown that a significant decrease in this low asymptomatic DVT risk results in a significant decrease in clinical pulmonary embolism.[10] However, the clinical efficacy of LMWH (i.e. in terms of symptomatic VTE) still remains to be demonstrated in general medical patients, since no single clinical trial has yet been sufficiently powered. The same conclusions can be drawn for acute ischemic stroke, especially in terms of the benefit-risk ratio, since LMWH must be evaluated in this case in association with antiplatelet drugs which have been shown to reduce stroke-related morbidity and mortality. The optimal LMWH dose regimen also needs to be discussed. The Medenox study clearly showed a dose-effect relationship with enoxaparin and the ineffectiveness of the lower prophylactic dose.[7] The recurrent question of the equivalence between the different LMWH should be solved before extrapolating the results obtained with enoxaparin to other LMWH. However, despite the need for additional clinical trials, there is already sufficient evidence to support the routine use of thromboprophylaxis in acute medical patients.

Second, the underuse of thromboprophylaxis directly concerns application of the clinical guidelines but publications of consensus conference recommendations alone are known to be insufficient to ensure the routine use of these guidelines.[11] The 6th ACCP Consensus Conference provided some rules for implementing thromboprophylaxis in a specific hospital based on a local evaluation and a local educational program.[8] In this context, the study by Ageno *et al.* could provide an exemplary procedure for increasing thromboprophylaxis in medical patients. Indeed the following prophylaxis implementation strategy can be proposed on the basis of this study:

- first, a prospective evaluation of thromboprophylaxis should be performed to identify underuse or overuse according to evidence-based medicine;
- second, some local consensus guidelines should be derived from the results of this prospective study and from evidence-based medicine;
- finally, a second study of thrombophylaxis use should be conducted to evaluate the impact of the local guidelines.

This strategy is clearly demanding, but VTE is an important health-care problem especially in medical patients, since more than 70% of symptomatic pulmonary embolisms occur without any previous surgical procedure. Such a strategy could increase the motivation of clinicians to identify VTE risk, and to adapt their practice to clinical guidelines they have personally contributed to establishing.

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References

1. Clagett GP, Anderson FA Jr, Levine MN, Salzman EW, Wheeler HB. Prevention of venous thromboembolism. Chest 1992; 102 Suppl 4:391S-407S.
2. Clagett GP, Anderson FA, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboembolism. Chest 1995; 108 Suppl 4:312S-34S.
3. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994; 343:886-9.
4. Clagett GP, Anderson FA Jr, Geerts W, Heit JA, Knudson M, Lieberman JR, et al. Prevention of venous thromboembolism. Chest 1998; 114 Suppl 5:531S-60S.
5. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. Thromb Haemost 1996; 76:529-34.
6. Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. Haemostasis 1996; 26:127-39.
7. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341:793-800.
8. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, et al. Prevention of venous thromboembolism. Chest 2001; 119 Suppl 1:132S-75S.
9. Ageno W, Squizzato A, Ambrosini F, Dentali F, Marchesi C, Mera V, et al. Thrombosis prophylaxis in medical patients: a retrospective review of clinical practice patterns. Haematologica 2002; 87:746-50.
10. Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost

2000; 83:14-9.
11. Stratton MA, Anderson FA, Bussey HI, Caprini J, Comerota A, Haines ST, et al. Prevention of venous thromboembolism: adherence to the 1995 American College of Chest Physicians consensus guidelines for surgical patients. Arch Intern Med 2000; 160:334-40.

Is there any role left for p210-derived peptide vaccines in chronic myeloid leukemia?

Despite the fact that the idea of *educating* the immune system against tumor-specific antigens by using an active immunotherapy such as a vaccine has been pursued by many researchers, consistent clinical data on the effectiveness of anticancer vaccines have not yet been produced. Lack of tumor specific targets, low immunogenicity of the tumor-associated antigens, inappropriate vaccine formulation and large tumor burdens of the vaccinated patients are some of the most frequent reasons accounting for the current disappointing results with anticancer vaccines.[1]

In chronic myeloid leukemia (CML), the chimeric p210 fusion protein resulting from the bcr-abl fusion gene produced by the t(9;22)(q34; q11) translocation, in virtue of the unique sequence of amino acids contained in the junctional regions, which is CML-specific, furnished the rationale for a peptide vaccine strategy in this disease.[2] In fact, peptides derived from amino acid sequences crossing the b3a2 breakpoint in p210, were shown to be able to bind to purified HLA class I and class II molecules with a binding affinity similar to that of naturally processed peptides and to elicit *in vitro* a specific T-cell response both in normal donors[3,4] and in CML patients.[5] In particular 4 peptides (8-11 amino acids in length) binding to the HLA class I molecules A3, A11 and B8 and one peptide (25 amino acids long) binding to the HLA class II molecule DR11 have been identified. The relevance of p210 peptides as tumor-associated antigens has been further confirmed by observing peptide-specific HLA restricted cytotoxic T-cells (CTL) and $CD4^+$ cells able to mediate killing of b3a2-CML cells and proliferation in the presence of b3a2 containing cell lysates, respectively.[6] The latter findings were the indirect proof of a *natural* CML cell processing of the fusion protein, presentation of junctional peptides on the cell surface within the groove of HLA molecules and recognition by T-cells.

Recently, the elution from HLA A3-positive CML cells of *KQSSKALQR*, one of the previously identified peptides, has finally proven endogenous presentation of breakpoint peptides onto class I molecules by CML cells.[7] In addition, the finding of HLA class II-restricted antigen presentation of endogenous bcr-abl fusion protein by CML-derived dendritic cells to $CD4^+$ T-lymphocytes suggests that CML cells can naturally process and present breakpoint-peptides also in the context of HLA class II molecules.[8]

Both these findings retrospectively furnished powerful scientific support for pursuing a breakpoint-peptide vaccine strategy in CML.

A short time ago, Scheinberg *et al.*[9] completed the first b3a2-breakpoint peptides phase I dose escalation vaccine trial in 12 patients with CML and b3a2 breakpoint. The multivalent peptide vaccine contained all 5 peptides previously described[4] associated with the immunologic adjuvant QS-21.[10] The patients' characteristics included hematologic remission, interferon-α (IFN-α) therapy and no HLA restriction.

The peptide vaccine appeared safe with 60% of patients experiencing only minimal discomfort at the site of injection. All but one of the patients enrolled had large tumor burden, however, the vaccine induced a peptide-specific delayed hypersensitivity (DTH) and a peptide-specific T-cell proliferation in 2/6 and 3/6 patients treated at the two highest dose levels of vaccine, respectively. It is noteworthy that the only patient vaccinated in cytogenetic remission had a transient disappearance of positivity for the b3a2 mRNA by reverse-transcription-polymerase chain reaction (RT-PCR).

More recently, a similar vaccine strategy was started at the Hematology Department of University of Siena, and in the attempt to improve vaccine immunogenicity and anti-tumor activity, in a HLA DR11 b3a2-CML patient in stable major cytogenetic response (MCR) we added to the peptide vaccine the same QS-21 adjuvant and low doses of granulocyte-monocyte colony-stimulating factor (GM-CSF) as co-immunoadjuvant.[11] The patient had obtained MCR (4/40) after 1 year of treatment with interferon (IFN)-α at 9MU/day plus cytarabine for 14 days/month, and did not improve any further despite continuing IFN-α treatment at 3 MU/day for another year. Two months before starting vaccinations, IFN-α was reduced to 3 MU/3 times a week, which she continued during vaccinations and thereafter. The vaccine consisted of a mixture of 100 μg/each 5 b3a2-derived peptides (4 binding to HLA class I A3, A11 or B8; and one binding to HLA class II DR11) plus 100 μg of QS-21. The day before peptide-QS-21 vaccination and for 4 consecutive days, GM-CSF (50 $\mu g/m^2$/day) was subcu-