A I S F
ASSOCIAZIONE ITALIANA PER LO STUDIO DEL FEGATO

Opinion of the Italian Association for the Study of the Liver (AISF) on the use of triple therapy (Peg-IFN + Ribavirin + first generation protease inhibitor) for the treatment of genotype 1 HCV patients with chronic hepatitis

The AISF Committee has developed Recommendations on the use of protease inhibitors in the treatment of HCV hepatitis in patients with genotype 1. The Recommendations have been classified according to the GRADE (1) criteria into 3 levels of evidence: A (high), B (medium), C low), and 2 levels of recommendation: 1 (strong), 2 (weak).

A bibliographic search was carried out in the following databases as at 1 December 2011:
- Medline/PubMed
- Embase (Excerpta medica)
- Database of Abstracts of Reviews of Effects

The recommendations represent a balanced summary of current evidence assessing benefits and risks attached to the use of protease inhibitors and will be updated annually as new knowedge becomes available in accordance with the above framework. They do not constitute a direct indication for prescription purposes or on how to use the drug, hence the reader is referred to the product fact sheet (PFS) contained in the package of each drug. Minor discrepancies (e.g. use of lower cut-offs for stopping administration) with respect to the indications provided by EMA and FDA are due to a prudential criterion chosen for the use of these rugs in a complex clinical context.
The final text was assessed by Experts who are not members of the Scientific Committee and who were asked to provide a critical evaluation. The members of the AISF committee and the Experts received no funds, no form of payment, reimbursement or any other form of direct or indirect remuneration for the drafting and reviewing the text, and they signed a declaration of conflict of interest highlighting any possible potential association (financial interest, research grants, participation in an advisory board, teaching assignments at sponsored educational events) with companies that have an interest in the production of antiviral drugs or diagnostic materials and instruments for the monitoring of therapy and disease. Disclosure criteria, recognized and commonly used at the international level have been applied. The list of the members of the Scientific Committee and of the Experts is included in Annex 1 and their conflict of interest in Annex 2.
The Text was submitted to EpaC – Patient Association, for their evaluation and opinions.

The potential benefit of a document produced by a Scientific Association is proportional to its quality, indeed appropriate methodologies and rigorous strategies in the development process are crucial for the correct implementation of clinical Recommendations.

The AISF Committee hence decided to have the quality of the document assessed by two external auditors through the Appraisal of Guidelines for Research & Evaluation (AGREE) (Annex 3) AGREE Next Step Consortium. AGREEII: checklist for evaluating the quality of the guidelines. GIMBE Foundation: Bologna, April 2011. Available on: Iwww.gimbe.org/agree. Last access 20/01/2012.

In order to express its position on the use of triple therapy (Peg-IFN+ Ribavirin + protease inhibitor) to treat patients with chronic hepatitis from genotype 1 HCV, the AISF Committee considered the following issues and relevant questions:

1. Treatment naïve patients
1.1 Who should be treated?
1.2 Can naïve patients be treated initially with Peg-IFN + ribavirin combination therapy?
1.3 What are the results of Peg-IFN + ribavirin + protease inhibitor triple therapy in naïve patients?
1.4 What factors are predictors of response to triple therapy?
1.5 In what patients is it possible to shorten the duration of triple therapy treatment?
1.6 What is the importance of the "lead-in" induction phase for Peg IFN + ribavirin combination therapy within the context of triple therapy?
1.6.1 Impact of lead-in on the efficacy of triple therapy
1.6.2 Initial lead-in phase and prediction of response to triple therapy

2. "Experienced" previous treatment-failure-patients
2.1 What are the results of triple therapy in previous-treatment-failure patients?
2.2 What factors are predictors of response to therapy?
2.3 Can treatment be shorter with triple therapy?
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2.4.2 Initial lead-in phase and prediction of response to triple therapy

3. Virological monitoring during triple therapy treatment
3.1 Monitoring of virological response
3.2 What are the criteria for stopping treatment?
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3.4 Practical management of treatment

4. Recommended doses and compliance

5. Management of adverse events
5.1 Anemia
5.2 Cutaneous side effects
5.3 Pharmacological interactions
5.3.1 Effects of other drugs on the pharmacokinetics of protease inhibitors
5.3.2 Effects of protease inhibitors on the metabolism of other drugs

6. Requirements for Centres that intend to treat patients with triple therapy using protease inhibitors

7. Otcomes indicators and pharmacoeconomic impact

1. Treatment naïve patients

1.1 Who should be treated?

The recent Recommendations issued by the European Association for the Study of the Liver (EASL) for the treatment of Hepatitis C suggest that a Peg-Interferon and Ribavirin combination therapy be administered to all naïve patients irrespective of their ammine-transferase values. Treatment should be started in all patients with moderate to advanced fibrosis (METAVIR score F2-F3-F4), while individually assessing the indication to treat for patients with mild fibrosis (METAVIR score F0-F1), especially in the presence of a long history of infection, and bearing in mind the effective incidence on life expectancy and possible new treatments in the future for these patients (2). With triple-therapy, benefits and risks are modified; on the one hand therapeutic efficacy in enhanced, while on the other, new side effects are possible, there is a risk of selecting resistant viral variants in the case of non-response, and there are additional costs due to the use of protease inhibitors.

Indications for triple therapy in patients with F0-F1 fibrosis must take into account the probability of progression of the fibrosis (3) and the possible presence of characteristics that predict a high probability of sustained virological response (SVR) with combination therapy (4). In the Hepatys study, the SVR rate in patients with genotype 1 was 69% in patients with F0 fibrosis, 44% in patients with F1-F2 and 31% in F3-F4 patients (5). In patients with moderate to severe fibrosis (F2-F4), it was demonstrated that the eradication of HCV is associated with a decrease in the risk of cirrhosis and hepatocellular carcinoma (6,7). In patients with compensated cyrrhosis, that are not very much represented in registration studies, little is known to date about any greater efficacy with respect to combination therapy and about safety.

Preliminary data obtained in France from the A.T.U. programs currently used (ETUDE ANRS CO20 CUPI, accessible at https://triton.u707.jussieu.fr/cupic/doc/COHORTE_ANRS_CO20_CUPIC.pdf) suggest that triple therapy is not well tolerated by these patients. There are contraindications against the use of both combination therapy and triple therapy in patients with uncompensated cirrhosis.

In symtomatic patients with cryoglobulinemia, it has been demonstrated that the eradication of HCV decreases the severity of symptoms (8). It is therefore conceptually logical to suggest a triple therapy for these individuals within the framework of specific trials. Given the risk of progression of the fibrosis in untreated patients, regular yearly monitoring is indispensable with the use of non-invasive fibrosis evaluation instruments (2).

Recommendations

- Availability of triple therapy does not change the range of indications for treatment in naïve patients with chronic hepatitis caused by HCV genotype 1, but it significantly modifies the mode of access and treatment management (C1). Treatment is aboslutely not applicable to patients with infections caused by HCV genotype non-1.

- Indications for antiviral treatment must be assessed in all naïve patients with chronic hepatitis C genotpe 1 (except in the cases on non-compensated cirrhosis) (A1).

- Indications for triple or combination therapy in naïve patients with chronic hepatitis C genotype 1

is to be assessed individually taking into account the factors that influence the probability of RVR and of SVR (B1).

- Triple therapy for the time being cannot be used for lack of clinical trials in patients with cryoglobulinemia, in patients with organ transplants, patients on dyalisis and in HIV co-infected patients outside clinical trials (A1). For these categories of patients, AISF emphasizes the extreme need for trials that assess its efficacy and safety.

- Treatment must begin as soon as possible in patients with severe fibrosis (F3-F4), and is indicated in patients with moderate fibrosis (F2) (B1).

- In patients with mild fibrosis (F0-F1), indication for treatment must be assessed on a case by case basis, taking into account both liver disease progression factors (age, gender, metabolic syndrome, necrotic-inflammatory activity), and symptoms, possible side effects of therapy and patient motivation (B1).

- Untreated patients must be monitored by doing biochemical tests and, where needed, through non-invasive evaluation of liver fibrosis at least once a year (A1).

1.2 Can naïve patients be treated initially only with Peg-IFN + ribavirin combination therapy?

The factors that predict response to combination therapy have been clearly identified. In patients with genotype 1 infection, they are represented essentially by age (< 40 years), level of viral load (<600,000 UI/ml), by the absence of severe liver fibrosis and by the absence of insulin resistance (2). Recently specific genetic polimorphisms of a nucleotid sequence located on chromosome 19 upstream from the gene of IL28B have been identified as being strongly associated with a sustained viral response (SVR) (9). The statistical weight of this parameter appears to be similar to that of the viral genotype. In patients with an HCV-1 infection and homozygous carriers of the CC genotype of the IL28B of caucasian origin (around 30% of patients infected with HCV) and without severe liver fibrosis, the percentage of SVR is estimated to be 86%, as against 36% and 43% found in patents with the TT and CT genotypes respectively (10). The study of viral kinetics indicates that an RVR is obtained in 30% of patients with CC genotype as against 5% of patients with CT or TT genotype.

In case of RVR irrespective of the IL28B genotype, the SVR possibilities are greater than 90%. There are no data that assess the efficacy of a 24-week combination therapy in CC patients with an RVR. In the absence of RVR, SVR is 60% in CC patients. Moreover, almost 80% of patients with an RVR have a CC genotype (10). By combining the figure relative to the genetic polimorhism of IL28B with the achieving of RVR, it is possible to identify a group of patients in whom a combination therapy of 48 weeks with Peg-IFN and ribavirin allows to obtain an SVR in 90% of cases and where the only advantage triple therapy has over the combination therapy is the shorter time required to eradicate HCV.

Recommendations

- Determining the IL28B genotype is useful to decide what treatment should be used in naïve genotype 1 patients with non-severe fibrosis (F0-F1-F2) (B1).

- In genotype 1 naïve patients with predictive factors of a positive response to treatment (CC genotype of IL28B and fibrosis < F3), the probability of eradicating HCV exceeds 80% with combination therapy which totally offsets or greatly reduces the greater eradication probability ensured by using triple therapy (A1).

1.3 What are the results of Peg-IFN + ribavirin + protease inhibitor triple therapy in naïve patients?

Boceprevir and telaprevir are two serine-protease NS3/4A inhibitors of the genotype 1 HCV virus; they are fairly powerful but they are endowed with a low genetic barrier. Phase II trials have demonstrated these molecules to be effective in combination with Peg-IFN + ribavirin in genotype 1 naïve patients, obtaining SVR rates of the order of 63% - 75% (11, 12). A detailed analysis is presented below of the results of Phase III trials.

Boceprevir
The SPRINT-2 trial assessed the efficacy of triple therapy with boceprevir + Peg-IFN2b + Ribavirin (13). 1089 patients were randomized to 3 groups: 1)Peg-interferon + Ribavirin (PR) combination therapyfor 48 weeks, 2) Boceprevir (BOC)-PR48 : initial phase with combination therapy (lead-in) for 4 weeks followed by 44 weeks of triple therapy, and 3) BOC-PR-Response Guided Therapy : 4 week lead-in followed by triple therapy whose duration depends on patient response. In this latter caregory patients with an eRVR (defined as negative serum HCV-RNA, determined with a PCR real-time technique at weeks 4 and 12) between W8 and W24 received 24 weeks of triple therapy, while patients without eRVR were given 24 weeks of triple therapy followed by 20 weeks of combination therapy. A severe fibrosis (F3-F4) was present in 9% of the patients. An SVR was observed more frequently in the BOC-PR48 groups (66%) and BOC-PR-RGT (63%), while it was 38% in the group receiving only PR.

Telaprevir
The ADVANCE trial assessed the efficacy of triple therapy, (TVR)+ Peg-IFN2a + Ribavirin, in 1088 patients randomized to 3 groups: PR48, TVR12-PR: 12 weeks of triple therapy, telaprevir + PR followed by 36 weeks of PR, and TVR8-PR : 8 weeks of triple therapy followed by 40 weeks of PR (14). In the case of eRVR (defined as negative serum HCV-RNA, determined with the PCR real-time technique), at weeks 4 and 12, the duration of treatment was shortened to 24 weeks for the two categories that received triple therapy. The percentage of patients with severe fibrosis was 20%. The percentages of SVR were significantly higher in the TVR12-PR (75%) and TVR8PR (69%) groups as againt the group with only PR48 (44%).

In summary the Phae III trials show that triple therapy with boceprevir and telaprevir are etter, with a 30% therapeutic gain across population of the trial versus combination therapy, and the possibility of decreasing treatment duration to 24 weeks in a subgroup of patients.

1.4 What are the factors that predict response to triple therapy?

The factors that predict SDVR were analysed in Phase III trials.

Boceprevir
In the SPRINT-2 trial, the factors that predict SVR were as follows as according to the multivariate analysis: ethnic group, viral load, age, absence of cirrhosis and statin therapy. SVR was more frequent in the absence of F3-F4 fibrosis (67% vs 52% in the BOCPR48). In the multivariate analysis, IL28B was confirmed to be an independent predictive factor of response (15). The percentages of SVR were 80% in CC patients, 71% in CT patients, and 59% in TT patients. Compared to combination therapy, a therapeutic gain was observed only in CT (41%) and TT(32%) patients, but not in CC patients (SVR: 78% vs 80%).

Telaprevir
For the ADVANCE trial, the results of the multivariate analysis are not yet available. In the univariate analysis, age < 40, female gender, absence of severe fibrosis, a BMI < 25 kg/m^2 and infection caused by genotype 1b versus 1a, were associated with SVR. The percentage of SVR was lower in the patients who presented an F3-F4 fibrosis compared to those in whom the fibrosis was classified as F0-F2 (62% vs 78% in the TRV12Pr group). Polymorphism of the IL28B gene was determined in 44% of patients; the percentages of SVR were respectively 90% in CC patients, 71% in CT patients, and 73% in TT patients (16). A therapeutic advantage between combination therapy and triple therapy was greater in the CT and TT patients rather than in CC patients (SVR difference: 50% vs 26%).

In summary, the factors that predict response in the triple therapy are the same as those of combination therapy but their weight seems to be weaker. Even in the presence of negative response factors (non CC IL28B, F3-F4 fibrosis) the possibilities of success are above 50% with triple therapy. In the case of positive response factors (CC IL28B and fibrosis < F3) the benefit afforded by triple therapy seems to be more limited (telaprevir) or even absent (boceprevir), given the high probability a priori of response to combination therapy. It must be pointed out that some population selection factors in the studies for registration of the two drugs, in particular the non universality of genetic screening for IL28B may reduce the strength of these prediction criteria in clinical practice.

Recommendations

• For genotype 1 naïve patients with pre-treatment negative response predictive factors (non CC genotype of IL28B or F3-F4 fibrosis), triple therapy should be envisaged as treatment of first choice (A1).

1.5 In what patients can triple therapy duration be shortened?

Phase III trials have looked into the efficacy of shorter treatment periods based on the trend of early viral kinetics.

Boceprevir
In the SPRINT-2 study an eRVR (negative HCV-RNA at week 8 maintained up to week 24) was observed

in 44% of patients. In this case, the possibilities of SVR were globally 96% in the two groups treated with boceprevir, while it was 72% if HCV-RNA was negative at least once between W8 and W24 and non detectable in W24. In the case of eRVR, the percentage of SVR was similar depending on whether the patients had received 28 or 48 weeks of treatment (96% vs 97%).

Telaprevir

In the ADVANCE trial, the patients treated with triple therapy all received treatment for 24 weeks in the case of eRVR (negative HCV-RNA at week 4 maintained up until week 12). In the TVR 12PR group, the possibilities of SVR were 89% vs 54% for patients without eRVR treated for 48 weeks. The ILLUMINATE trial included 540 patients who received triple therapy (Peg IFN2a, Ribavirin and telaprevir) for 12 weels followed by 12 weels of combination therapy (aggiornare biblio con riferimento di NEJM aggiunto 17). On W24, the patients who had achieved an eRVR, were randomized: in the first group (TVR12PR12), treatment was interrupted while the second group (TVR12PR36) was given combination therapy for an additional 24 weeks. eRVR was obtained in 63% of the patients. The percentage of SVR was 92% in the group that received treatment for 24 weeks while it was 88% in the group treated for 48 weeks.

The results of these trials cleary indicate that once an eRVR is obtained with telaprevir or with boceprevir, the possibilities of success are very high, of the order of 90%, and therefore a short treatment of 24 (telaprevir) or 28 (boceprevir) weeks is sufficient. On the other hand, the probability of obtaining an RVR, and hence short treatment, is higher in CC IL28B patients than in CT or TT patients (89% vs 52% in the SPRINT-2 trial). The presence of a severe fibrosis (F3-F4) could on the other hand alter the possibility of success in patients with eRVR and short treatment. In the ILLUMINATE trial the percentage of SVR was 82% in F3-F4 patients treated for 24 weeks, and 88% in those treated for 48 weeks. In the SPRINT-2 trial the percentages of SVR in F3-F4 patients was 75% for patients treated for 28 weeks vs 92% for those treated for 48 weeks (18). The probability of obtaining an eRVR in F3-F4 patients was low and it must be pointed out that these percentages refer to small groups of patients and hence an appropriate statistical analysis was not possible.

Recommendations

- In patients who obtain an eRVR, the probability of SVR is very high and short treatment (28 weeks with boceprevir and 24 weeks with tepalrevir) proves to be sufficient (A1)

- In the case of severe fibrosis (F3 or F4), even if an eRVR is present, the possibilties of SVR are reduced by a high incidence of recurrences that makes it necessary to exted treatment to 48 weeks (C2).

1.6 What is the importance of the "lead-in" induction phase for Peg-IFN + Ribavirin combination therapy within the context of triple therapy??

1.6.1 Impact of lead-in on the efficacy of triple therapy

In naïve patients, the impact of lead-in on the efficacy of triple therapy is based on a single trial. It is a Phase II trial (SRINT 1) that compares the efficacy of triple therapy with boceprevir with or without the lead-in phase during 24 or 44 weeks of treatment versus standard treatment (12). Even though the goal of this trial was not that of comparing treatment groups with or without a lead-in phase, the analysis of the results suggests that the rate of SVR is not significantly different within the 4 groups of treatment with boceprevir: 56% (IC 95%: 46-66%) versus 54% (IC 95%: 44-64%) for 24 weeks of triple therapy and 75% (IC 95%: 65-83%) versus 67% (IC 95%: 57-76%) for a triple therapy of 44 weeks. The rates of viral breakthrough was not significantly influenced by the lead-in phase (4 vs 7% and 5 vs 12%, $p>0.05$). On the other hand, the RVR rate during triple therapy was significantly higher in the groups with lead-in phase versus those that without lead-in (62% vs 38%, $p<0.001$). The latter result suggests that the lead-in phase could allow a higher number of patients to benefit from a short 28-week treatment. There are no lead-in data on triple therapy with telaprevis in naïve patients.

51.6.2 Initial lead-in phase and prediction of response to triple therapy

The initial lead-in phase assesses patient sensitivity to combination Peg-interferon/Ribavirin therapy that conditions the efficacy of triple therapy, given the rapid onset of resistance-induced viral mutations when the protease inhibitor acts in conditions of "functional monotherapy".

In the SPRINT-2 trial, the reduction of the viral load at the end of the lead-in phase was analysed. The percentages of SVR were 28% and 43% in patients with a viral load decrease < 1 log UI/mL, while they were on the order of 80% in patients with a viral load lowering > 1 log UI/mL (13).

An unchanged viral load (1log UI/mL) at the end of the lead-in phase was strongly predictive of the selection of resistant viral variants in patients who had not eliminated the HCV-RNA during triple therapy (68% vs. 31%, $p<0,001$).

The further evaluation of the L28B genotype did not improve response significantly (15). The predictive value of initial lead-in phase plus fibrosis severity was not analysed. In the multivariate analysis, the decrease in HCV-RNA during the initial lead-in phase was the only independent predictive factor of SVR (18). There are no data on the initial lead-in phase in naïve patients treated with triple thaìerapy with telaprevir.

Recommendations

- In naïve patients treated with boceprevir who were found to have an HCV-RNA reduction > 1 log UI/ml at the end of the lead in phase, the probability of having an eRVR with triple therapy is significantly greater than two-drug therapy which means that treatment can be cut down to 28 weeks (B1).

- In naïve patients treated with boceprevir with a viral load decrease < 1 log UI/mL at the end of the initial lead-in phase, the likelihood of success is less and the risk of selecting resistant viral strains is higher. Triple combination therapy with boceprevir should be considered for this class of patients only after having carefully assessed their risk-benefit ratio (B2).

- The use of the lead-in phase was not studied in naïve patients treated with triple combination therapy with telaprevir. It is therefore not possible, as indicated in the fact sheet, to use this approach as a sensitivity test to combination therapy in this context. (A1).

2. Previous-treatment-failure patients

2.1 What are the results of triple therapies in previous-treatment-failure patients?

In genotype 1 patients, in whom combination Peg-IFN + Ribavirin therapy failed, retreatment with combination Peg IFN + Ribavirin therapy entails an SVR of 23% in relapsers and 6% in non-responders (19). Therapeutic optimization that seeks to adapt the doses of Peg-IFN and/or Ribavirin and the duration of treatment offers a little benefit.

Telaprevir
According to the PROVE 3 Phase II trial that used telaprevir in combination with Peg-Interferon and Ribavirin therapy in patients in whom treatment had failed, the percentage of SVR in the triple therapy groups was of the order of 50% (20).
In the REALIZE trial, 650 relapsers, partial responders and non-responders were randomized to three groups: a group treated with PR for 48 weeks, a group that received triple therapy with telaprevir for 12 weeks followed by 36 weeks of combination therapy, and a group that was put on an initial lead-in phase for 4 weeks with Peg-Interferon and Ribavirin, followed by 12 weeks of triple therapy with telaprevir, followed by further 32 weeks of combination therapy (21). Total duration of treatment was 48 weeks for all patients. Almost half of the patients presented severe fibrosis (F3-F4). Triple therapy proved to be significantly more effective than combination therapywith SVR rates of 66% in those who had been through a lead-in phase with Peg-Interferon + Ribavirin for 4 weeks, 64% in patients without the lead-in phase, and 17% in the control group who had been on combination therapywith Peg-Interferon and Ribavirin.

Boceprevir
In the RESPOND-2 trial, 403 relapsers and partial responders to previous treatment were randomized to 3 groups: a control group that received only Peg-Interferon and Ribavirin for 48 weeks, a group that had a lead-in phase with only Peg-Interferon – Ribavirin for 4 weeks followed by 44 weeks of triple therapy with boceprevir, and a response-guided treatment group (RGT) for whom duration varied depending on early virological response (22). In this third group, treatment was interrupted on W36 if eRVR was achieved. In the absence of eRVR, boceprevir was stopped at W36 and combination therapy continued until W48. Triple therapy proved to be significantly more effective than combination therapy with SVR percentages of 66% (BOC-PR48) and 59% (BOC-PR-RGT) versus 21% for patients in the control group.

2.2 What factors are predictive of response to triple therapy?

The predictive factors of patient response to treatment were evaluated in Phase III trials. In the two REALIZE and RESPOND-2 trials, the response profile to prior treatment was found to be the most effective predictive factor. In the REALIZE trial, the percentages of SVR matched the patterns of failure to respond to previous treatment. Triple therapy (respectively with and without lead-in) was effective in 83% and 88% in relapsers, in 54% and 59% in partial responders, and in 33% and 29% in non-responders. In the RESPOND-2 trial, SVR percentages in the BOC-PR48 and BOC-PR-RGT groups were respectively 75% and 69% in relapsers, and 52% and 40% in partial responders. Stage of fibrosis was the second independent factor associated with SVR. In the REALIZE trial, global results in terms of SVR in the triple therapy groups were 74% in patients with F0-F2 fibrosis, 66% in patients with F3 fibrosis, and 47% in patients with cirrhosis. In relapsers the stage of fibrosis had no impact on SVR (F0-F2: 86%, F3: 85%, F4: 84%). Instead the weight of fibrosis on SVR was greater in partial responders (F0F2: 72%, F3: 56%, F4: 34%) and in non-responders (F0-F2: 41%, F3: 39%, F4: 14%). .

Therefore, the patients that are most difficult to treat with triple therapy are cirrhotic patients who have not responded to previous treatment, with SVR percentgaes below 15%, and without any significant difference from the control group. Also in the RESPOND-2 trial, fibrosis had a greater impact on SVR that varied in the group on triple therapy between 66% and 68% in patients with F0-F2 fibrosis versus 44%-68% in patients with an F3-F4 fibrosis (18). Other factors such as viral sub-type were associated with SVR in the REALIZE trial, with SVR percentages that were globally 59% in genotype-1a patients versus 71% for genotype-1b. Instead, in both trials, IL28B polymorphism had no significant impact on SVR (16,23). In summary the response profile to previous treatment is the main predictive factor of response to triple therapy. Also in the case of no previous virologic response, the results with telaprevir are of the order of 30% SVR. In these patients, the efficacy of triple therapy must be carefully assessed together with the medium term prognosis of liver disease (as the probabilities of SVR are inversely correlated to the severity of the fibrosis), the side effects of triple therapies, economic costs and the possibility of combination with antivirals in the medium term that allow for better results and perhaps shorter and better tolerated tgreatment.

Recommendations

- Triple therapy with Peg IFN, Ribavirin, boceprevir or telaprevir is currently the treatment of reference for patients who failed Peg-Interferon and Ribavirin combination therapy, (B1) .

- Patients who relapsed after combination therapy must start triple therapy as soon as possible if they also have severe fibrosis (F3-F4); it is indicated also in patients with mild fibrosis (F2). For patients with minimal lesions (F0-F1) it should be discussed on a case-by-case basis (B1).

- Since in the case of non-responders to combination therapy, triple therapy with Telaprevir produced an SVR only in 15% of the patients with an F4 fibrosis and in 40% of patients with an F3 fibrosis, its use needs to be carefully assessed on the basis of a risk-benefit ratio. Similar remarks can be made for triple therapy with Boceprevir, in spite of the fact that the definition of non-responders to combination therapy, in this case, was made not on the basis of patient history but on the basis of viral kinetics observed during the lead-in phase. For patients with F0-F2 fibrosis, the risk-benefit ratio needs to be assessed on a case-by-case basis (B2).

- In non-responders to combination therapy who have severe fibrosis, SVR can be achieved only in 15% of F4 patients and in 40% of F3 patients with triple therapy that includes telaprevir (these patients were excluded from trials with boceprevir). For patients with F0-F2 fibrosis, the risk-benefit analysis must be made on a case-by-case basis (B2).

2.3 Can treatment be shorter with triple therapy ?

The possibility of shortening the therapeutic regimen of triple threrapy in patients with previous treatment failure to combination therapy with Peg-IFN and Ribavirin was evaluated only with boceprevir in the RESPOND-2 trial. In this trial, after the initial lead-in phase, the patients in the BOC-RGT group with an eRVR received triple therapy shortened to 32 weeks, for a total treatment period of 36 weeks. In this group an eRVR of 46% was observed and the percentage of SVR was 86%, comparable to the 88% observed in the group of patients treated with triple therapy for 44 weeks. A shorter treatment period of 36 weeks therefore seems possible for patients with an eRVR. In the absence of eRVR an additional Peg IFN + Ribavirin combination therapy was delivered for 12 weeks to the BOC-PR-RGT group. The percentage of SVR is similar to that observed in patients without eRVR treated for 44 weeks with triple therapy (40% vs 43%). Instead, in patients with severe fibrosis (F3 and F4), the SVR percentage is globally lower in the BOC-RGT groups versus the group subjected to fixed treatment duration (44% vs. 68%).

Recommendations

- In patients in whom Peg-IFN + Ribavirin combination therapy has previously failed, if they are retreated with boceprevir and obtain an eRVR, the probability of SVR is very high and a brief treatment period of 36 weeks is sufficient (4 weeks of lead-in followed by 32 weeks of triple therapy) (B1).

- In cases of severe fibrosis (F3 and F4), even if an eRVR is obtained, the possibilities of success are probably less if treatment time is shortened. 48 weeks of treatment are recommended (initial lead-in phase of 4 weeks followed by 44 weeks of triple therapy with boceprevir) (A1).

- There is no scientific evidence that supports the indication of shorter treatment duration in previous-treatment-failure patients retreated with triple therapy with telaprevir (B2).

2.4 In what way is the initial "lead-in" phase with combination therapy before triple therapy important?

2.4.1 Impact of the initial lead-in phase on the efficacy of triple therapy.

In previous-treatment-failure patients, the importance of the initial lead-in phase with combination therapy was assessed only in patients treated with triple therapy with telaprevir. In the REALIZE trial there is no difference in SVR between patients treated with or without lead-in phase, whether they were relapsers (88% vs. 83%), partial responders (54% vs. 59%) or non-responders (33% vs. 29%). The percentage of RVR obtained after 4 weeks of triple therapy is higher in non-responders who had a lead-in phase, but this benefit does not produce an increase in SVR in this sub-group. The breathrough

percentage under treatment is similar depending on whether there was or there was not a lead-in phase in relapsers (1% vs. 1%) and in partial responders or non-responders (17% vs. 19%). Frequency in the selection of restistant mutations is similar whether patients with previous treatment failure had or did not have a lead-in phase (21).

2.4.2 Initial lead-in phase and predicting response to triple therapy

As occurred with the naïve patients who were treated, the lead-in phase serves to assess the efficacy of triple therapy. In patients treated with telaprevir in the REALIZE trial, the SVR percentages, depending on whether the decrease in viral load at the end of the initial phase was greater or lower than the threshold of 1 log UI/mL, were 54% vs. 15% in non responders, 59% vs. 56% in partial responders and 88% vs. 62% in relapsers. In the same fashion, in patients treated with boceprevir in the RESPOND-2 trial, the SVR percentages at the viral load threshold of 1 log UI/mL at the end of the initial phase with combination therapy, were 61% vs. 73% in partial responders, and 81% vs. 37% in relapsers.
These data indicate that response to the lead-in phase makes it possible to assess efficacy of triple therapy, even though it cannot replace the response profile to previous treatment that preserves an independent predictive value, and to which it is complementary. The size of the response obtained in the initial phase with combination therapy is even more important for the fact that sensitivity to interferon in a patient may evolve in time for multifactorial causes that include the progression of fibrosis, age, necrotic –inflammatory activity or the onset of insulin resistance. Moreover, it is difficult at times to be able to determine with certainty the profile of the previous response since these data, even where they do exist, are often incomplete or not available. This is particularly important for non-responders in whom SVR obtained with a regimen than includes telaprevir is greater than 50% if the decrease in viral load at the end of the lead-in phase is greater than 1 log, and is only 15% (probably between 5% and 10% in the case of F3-F4 fibrosis) in patients with a decrease in viral load of less than 1 log.

Recommendations

- If it is not possible to determine the profile of response to previous treatment, an initial lead-in phase helps predict the efficacy of triple therapy (B1).

- In relapsers or partial responders to previous treatment, response to the initial lead-in phase makes it possible to predict response to triple therapy with boceprevir (B1).
- In patients with previous therapeutic failure retreated with triple therapy with telaprevir, the initial leaed-in phase does not improve the SVR percentages and does not prevent the onset of resistant variants (B1):
- In non-responders treated with triple therapy with telaprevir, the initial lead-in phase with combination therapy is useful to assess the possibility of success of triple therapy and hence it should be used systemativcally. If the decrease in viral load is less than 1 log UI/mL, the probability of success is very poor and the risk-benefit ratio of continuing treatment should be carefully examined (C2).

3. Virological monitoring during triple therapy treatment

3.1 Monitoring the virological response

Treatment efficacy monitoring is based on repeated measurements of the viral load. This must be determined using a sensitive quantification method represented by a real-time PCR test with a low quantification threshold (limit of detection, LOD: ≤ 10 UI/ml). The same method must be used at the beginning and throughout patient monitoring. The viral load must be measured on the first day of therapy, before administering the drugs, then at a frequency that has been defined in the therapeutic protocols of boceprevir and telaprevir in accordance with the authorization issued by EMA in 2011 and indicated in their respective fact sheets. Taking into account the kinetics of the very rapid viral drop during the first two weeks of triple therapy, it is important to check the viral load on week 8 (W8) after starting treatment with triple therapy in order to assess any early viremia "blip" (transient rebounds of viral load) that might be overlooked if the first check is done on week 4 (W4) from the start of treatment. Subsequent viral load checks are to be made as indicated in the registration data (Figure 1). In the case of triple therapy with telaprevir, measuring the viral load on week 16 (W16), that is to say 4 weeks after interrupting telaprevir, is useful to identify the viremic blips caused by the transition to combination therapy.
In general it is important to monitor the viral load every month, until it can be detected during triple therapy, so as to identify any early viremic blips linked to mutations in resistance to protease inhibitors. The definition of a non-detectable HCV-RNA is however difficult and needs international consensus. In Phase III trials HCV-RNA is considered to be non-detectable when it is lower than 25 UI/ml in the trials with telaprevir and if less than 9.3 UI/ml in the trials with boceprevir. In clinical practice, it is therefore difficult to interpret an HCV-RNA below the quantification threshold even if it is detectable. A difficulty due to practical reasons is related to the timing in obtaining the HCV-RNA result from the laboratory. Except for some centres, it is impossible to obtain the result in less than 24 hours. The therapeutic decision is therefore postponed by a couple of days while waiting for the virology results, an aspect that is to be taken into account when planning organizing patient treatment.

Recommendations

- A sensitive detection test (lower detection limit < 25 UI/ml, linear quantification up to the threshold/limit), preferrably a real-time PCR test, must be used for the virological monitoring of triple therapy (A1).

- Additional control of the HCV RNA two weeks after the start of triple therapy is useful to identify the early viremic blips (C2).

- L'HCV-RNA must be checked monthly until the viral load is detectable, and then every three months thereafter (C2).

3.2 What are the criteria for interrupting treatment?

The rules for stopping treatment in the Phase III trials described above vary depending on the status of the patients (naïve or in therapeutic failure) and depending on the molecule used. They are summarized in Table 1.

It must be noted that these interruption rules were defined a priori in the trials, probably with a view to preventing resistant mutations. Since these interruptions rule have not yet been assessed, it is currently impossible to judge their validity in clinical practice.

However, during the trials, transient rebounds were observed in the viral load («blips») however without them influencing the SVR. Whether combination therapy should be continued is to be assessed on a case-by-case basis depending on the monitoring period and on the viral load.

Table 1: Rules for stopping treatment

	Naïve Patient	Treatment failure patient terapeutico
Telaprevir	*W4: HCV-RNA > 100 UI/ml → STOP Telaprevir, continue °PR	*W4 and W12: HCV-RNA > 100 UI/ml → stop telaprevir
	*W12: detectable HCV-RNA → stop Telaprevir and °PR	*W12: HCV –RNA > 100 UI/ml → stop °PR
	*W24-: detectable HCV-RNA → stop °PR	*W24: detectable HCV-RNA → stop °PR
Boceprevir	*W24: detectable HCV- RNA → stop Boceprevir and °PR	*W12: detectable HCV-RNA → stop Boceprevir and °PR

*W= Week
° PR = Peg-Interferon and Ribavirin

Recommendations

- In triple combination therapy the rules (and the threholds/limits) for stopping treatment were defined a priori and arbitrarily in the trials, and may turn out to be too restrictive or not optimal. However, given the lack of trials that check their validity in clinical practice, we need to comply with the instructions provided in the fact sheet of Boceprevir and of Telaprevir adding some time points to the detection of HCV-RNA required to better assist the clinician in his decision to stop therapy, by keeping to a safe cut-off (100 UI/ml) (C2).

3.3 How should we assess resistance to protease inhibitors?

Resistance against first generation protease inhibitors is conferred by a relatively large number of aminoacid substitutions. These substitutions confer cross-resistance to all first generation protease inhibitors. Some of these mutations, in particular those obtained in the 1a viral sub-type could be crossed over with those of the second-generation protease inhibitors. The replacement of amminoacids confers resistance to the protease inhibitors in the form of minority viral populations in all patients who are naïve to protease inhibitors. The administration of a protease inhibitor selects the viral variants that carry pre-existing mutations that cross over in an exponential manner up until they become majority in the case in which treatment is continued. Failure (persistence of HCV-RNA) in the case of triple therapy that includes a protease inhibitor is essentially linked to an insufficient response to IFN and to Ribavirin. The growth of viral populations that are resistant to the protease inhibitors is therefore a consequence and not the cause of the poor efficacy of the treatment. In Phase III trials, half of the patients in treatment

failure presented viral populations that were resistant to telaprevir or to boceprevir at the time of the blips or of a rebound of the HCV-RNA.
The decrease in viral populations resistant to telaprevir or to boceprevir starts when the administration of the protease inhibitor is stopped. This phenomenon is slow and after several months or years leads to the substitution of the minority resistant variants with a majority viral population that is sensitive to the protease inhibitors, re-establishing a situation similar to that observed before treatment. The long-term impact of resistance is unknown. Only an analysis of the response to future treatment that uses new protease inhibitors with crossed resistance can tell what therapeutic impact is produced by these long-term resistance mutations. At present the sensitivity of the tests that detect the resistance mutations, and of sequencing, is insufficient. In these trials the non-detection of mutants does not mean absence of resistance. More sensitive detection techniques as for instance pyro-sequencing, are still only used for research purposes.

Recommendations

- Currently there is no indication in clinical practice of any indication for searching the viral variants that are resistant to telaprevir or boceprevir at the beginning of treatment. Any reappearance of HCV RNA detected during triple combination treatment, if not linked to low adherence, is to be considered as surrogate evidence of pharmacoresistance (C1).

- Switching to boceprevir, telaprevir or to telaprevir is not possible in the case of resistance or intolerance (B1).

3.4 Practical management of treatment

The practical management of treatment with telaprevir or boceprevir must take into account the predictive response factors, in particular an evaluation must be made of the stage of the fibrosis, the treatment history of the patient, whether naïve or experienced, and the viral kinetics during treatment. In Tables 1 and 4 monitoring algorithms are proposed that correspond to the main clinical situations. The interruption criteria proposed differ to some extent from those that were used in the clinical trials.

4. Recommended doses and treatment compliance

The recommended dose of boceprevir is 800 mg every 7-9 hours, which corresponds to twelve 200-mg capsules per day to be taken during meals. The recommended dose of telaprevir is 750 mg every 8 hours, which corresponds to six 375-mg capsules per day to be taken during meals. The dose of the protease inhibitor must not be reduced because this would facilitate the appearance of resistant strains and would lead to therapeutic failure. It is therefore of the utmost importance to educate the patient in order to ensure compliance. A retrospective analysis of Phase III trials with boceprevir shows that compliance with the duration of treatment (>80 %, <80 %) has a significant influence on the percentage of SVR (24). Instead forgetting some doses of boceprevir does not seem to have any impact on SVR. In the same way, if duration of treatment is not complied with, failure to comply with the 7-9 hour interval between the two administrations once does not seem to have any influence on the SVR. These data have not been confirmed yet for telaprevir.

Recommendations

- The dose of protease inhibitors must never be decreased (A1).
- In triple therapy it is imperative to comply with the prescribed duration of treatment (A1).

5. Management of adverse effects

5.1 Anemia

Triple therapy with boceprevir or telaprevir increases the risk of anemia by about 20% compared to combination therapy with Peg-Interferon and Ribavirin (9, 10). The percentage of patients with anemia, defined by a hemoglobin <10 g/dl, is about 50% with triple combination therapy with boceprevir and 40% with triple combination therapy containing telaprevir. Treatment interruptions due to anemia are however rare. In the trials with boceprevir, the use of erythtropoietin (EPO) was recommended and actually administered in 43% of patients. Instead, in the trials with telaprevir, the use of EPO was not allowed. Retrospective analyses of Phase III trials with boceprevir and telaprevir demonstrate that the decrease in the dose of ribavirin does not appear to have a negative impact on the SVR (25, 26). Moreover, the use of EPO does not appear to have a positive impact on the SVR. The data obtained from these trials on triple combination therapy must however be weighed against the retrospective trials carried out on a high number of patients treated with Peg-IFN and Ribavirin combination therapy. These trials demonstrate that the decrease in the dose of ribavirin has a negative impact on SVR only when the cumulative dose is lower than 60% of the envisaged dose. Moreover, if the derease in the dose occurs at the moment in which the HCV-RNA is not detectable, the impact on the SVR appears to be minimal (27). Using EPO makes it possible to maintain the entire dose of ribavirin more often and improve quality of life (28). In a post hoc analysis of a controlled trial that included more than 3000 patients, it was demonstrated that the patients who developed anemia during combination therapy, had a higher rate of SVR compared to the patients who did not develop anemia (29). In this trial, EPO increased the chances of SVR only when it was administered during the first 8 weeks, hence probably at a time when HCV-RNA was still detectable. If anemia appears when HCV-RNA is not detectable the dose of ribavirin may be decreased progressively by 200 mg.
Recommendations

- If the anemia appears when the viremia is still detectable, the dose of Ribavirin must be maintained. The dose reduction of Ribavirin must be the first action in case of anemia, reserving the use of EPO, if any, only to selected cases, where the reduction of Ribavirin is not sufficient to control the anemia. In any case EPO may be used according to the AIFA Recommendations currently in force in our Country (B1)
- If the anemia appears when the viremia is not detectable, the dose of Ribavirin may be decreased. In this situation the use of EPO must be discussed on a case by case basis. (C2).

5.2 Cutaneous side effects

The cutaneous side effects of interferon and of Ribavirin are well known. Excluding the skin reaction at the injection site, the administration of interferon is associated in 10% of cases with the appearance of

an erythematous, dry (xerosis) and itchy skin that may lead to diffused excematous pruritis. This side effect that may vary in intensity and is subjective, is compatible with the continuation of the treatment; the lesions disappear progressively when treatment is stopped. The administration of ribavirin is associated in 30% of cases with the onset of an erythematous skin, with xerosis and pruritus especially in the skin folds, which often leads to diffused pruritus.
This eczematous dermatitis is more severe than the one that appears during treatment with interferon alone. This symptom, that is not well tolerated by patients, may require recourse to a dermatologist throughout the duration of treatment. Other rare manifestations have been described with Ribavirin, which include pigmentation, lichenoid eruptions and exceptionally, the Stevens-Johnson's syndrome (SJS). Treatment with telaprevir used in triple combination therapy is associated in 54% of cases with the onset of skin manifestations. In more than 90% of cases it arises during the first month of treatment. Erythema and xerosis are the most common side effects.
Poorly delineated excematous vesicular lesions are associated with pruritic lesions and multiple excoriations. The neck and the axilla are the areas most heavily affected. In more than 90% of the cases the body surface involved does not exceed 30% and the eruption is classified as 1st degree (localized) or 2nd degree (diffused across <50% of the skin). In less than 10% of cases the manifestations are classified as 3rd degree (greatly diffused >50% of the skin surface). It may also be an eczematous dermatitis whose diffusion on the body surface exceeds 50% and/or the presence of other heterogeneous skin manifestations: vesicles, skin or mucous bubbles, pustules, purpura, mucous ulcers that must suggest either an SIS or a DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) that generally have a late onset after the sixth weel of treatment. Up to the present time e11 cases of DRESS and 3 cases of SIS have been found out of a total of 3000 patients who were administered telaprevir within the framework of clinical trials.

Treatment with telaprevir may be continued in the presence of a localized dermatitis or a grade 1 dermatitis without itching. The opinion of a dermatologist is not indispensable. Treatment with telaprevir may be continued in the presence of a grade 2 dermatitis following the opinion of a dermatologist who ensures regular follow-up. The extent of the eruption or other skin involvement warrants discontinuation of telaprevir. The absence of improvements after one week entails the discontinuation of ribavirin. Treatment with telaprevir is to be definitely discontinued in the presence of a grade 3 eruption. Where there is suspicion of SJS or DRESS all treatment must be stopped and the patient immediately hospitalized.

Recommendations

- During treatment with telaprevir, the opinion of a dermatologist is necessary for grade 2 skin lesions (A1).

- During treatment with telaprevir, there may be severe skin lesions (DRESS or Stevens-Johnson's syndrome) that need early recognition. They require that triple therapy be stopped immediately and the patient must be hospitalized (A1).

5.3 Pharmacological interactions

Boceprevir, and above all telaprevir, are metabolized through cytochromes P450 3A4 and 3A5 (CYP3A4/5). Moreover these two protease inhibitors have a strong inhibiting action on the P450 cytochrome family that constitutes more than 30% of the total P450 cytochrome in the liver. Consequently there are risks of interaction with other drugs that are metabolized along the same pathways with the

possibility of having 4 different pharmaco-clinical situations.

5.3.1. Effects of other drugs on the pharmacokinetics of protease inhibitors

5.3.1.a. Induction of CYP3A with a lowering of the plasma concentration of protease inhibitors and the risk of losing therapeutic efficacy and the possible development of resistant mutants. The main 'indicted' inductors are rifampicin, rifabutin and hypericum (St. John's wort) that must not be administered. For other less powerful inductors like phenytoin, carbamazepine, phenobarbital or dexamethasone, the risk is minimal. Their use must be weighed against the benefits they can provide.

5.3.1.b. Some medicinal products are competitive or non-competitive inhibitors of CYP3As and induce a decrease in the metabolism of telaprevir and boceprevir exposing patients to the risk of overdoses that may induce side effects. These medicinal products are mainly antifungals like, first and foremost, ketoconazole that is contraindicated. Other antifungals from the same family may equally be involved: itrakonazole and posakonazol. Methoxalene and cymetedine, powerful non-competitive inhibitors, are contraindicated. Grapefruit, that is an inhibitor of CYP3A, must be avoided. For other drugs like macrolids, the inhibiting effect is limited to telaprevis and is not significant for boceprevir.

5.3.2. Effects of protease inhibitors on the metabolism of other drugs

5.3.2.a. An inhibiting effect on cytochrome by the protease inhibitors may turn into an overdosage of other drugs having the same metabolic pathway. The risk is particularly high for drugs with a low therapeutic index. Especially class I and II antiarrhythmics come under this effect: amiodarone, flecainide, propaphenone, quinidine and bepridil may expose the patient to a lengthening of the Q-T interval and to risks of peak torque. In the same way, inhibition of the by-products of ergot (di-hydroergotamine, ergotamine, etc.) may entail severe risk. Benzodiazepin like midazolam i.v. are equally contraindicated as are other drugs like sildenafil and cisapride. As regards statins, contraindications are not absolute. However, the use of simvastatin and lovastatin is not recommended. Other drugs undergo less important effects as for instance lidocain, digoxin, warfarin or anti-hypertensive drugs of the calcium-blocker family and immune-suppressors like cyclospporin and tracrolimus. However pharmacokinetics needs to be controlled as do dosage adjustments.

5.3.2.b. The concomitant use of protease inhibitors entails a possible increase in the speed of elimination of some drugs and therefore the lowering of their effective plasma concentration: e.g. ethynilestradiol (attention to the risk of reducing the efficacy of oral contraception), escitalopram, desipramine, zolpidem. Finally it is important to highlight the fact that for some drugs it is not necessary to change the dose a priori because there are no significant interactions; e.g. buprenorfin, methadone, tenofovir and exomeprazol .

Recommendations

A careful analysis of associated treatments needs to be made to avoid interactions related to CYP3As (especially some anti-arrhythmic drugs). It is very useful to consult the online services on interactions (www.hep-druginteractions.org) before prescribing drugs while patients are on treatment with boceprevir and telaprevir and explore the possibility of alternative treatment using medicines that are not metabolized by the CYP3As (B1)

6. Requirements of the centres where triple combination therapy with protease inhibitors is administered

Recommendations

The centres where this therapy is administered must:

1) Make quantitative measurements of serum HCV-RNA using the PCR-real-time method to promptly provide results so that therapeutic decisions can be made;

2) Study the polymorphism of the IL28B gene;

3) Have the competences to adequately assess pharmacological interactions

4) Have a dermatologist of reference with expertise in the management of the side effects of these drugs.

7. Outcome indicators and pharmacoeconomic impact

These Recommendations aim at improving appropriate use of medicinal products and do not imply any increase in pharmaceutical spending; they are a tool to rationalize spending and make savings especially for naïve patients. It woud be desirable to monitor the Recommendations by setting up a data base/register containing information on treated patients. By processing the data contained in the register it will be possible to assess outcomes on the use of the drugs (e.g. % patients with SVR) and make relevant pharmacoeconomic evaluations.

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Annex 2

Statement of conflict of interest

Author/Editor	Pharmaceutical/diagnostic Company	Role
Raffaele Bruno	Janssen	Member of advisory board, trainer at sponsored educational events
Paolo Caraceni	NA	NA
Barbara Coco	NA	NA
Mirella Fraquelli	NA	NA
Giovanni Squadrito	NA	NA
Pierluigi Toniutto	MSD	Member of advisory board, trainer at sponsored educational event
Alfredo Alberti	Roche, Merck, Gilead Roche, Novartis, Gilead, Merck, BMS	Research grant Advisor and sponsored speaker
Ferruccio Bonino	NA	NA
Massimo Colombo	Merck, Roche, BMS, Gilead Science Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex	Grant and research support: Advisory committees: Speaking and teaching:
Antonio Craxì	Merck Sharp & Dohme Janssen Cilag Vertex Anadys Genentech Bristol Myers Squibb Gilead Achillion Boehringer-Ingelheim Enzo Biochem Tibotec Roche Abbott Inhibitex Pharmasset Novartis ScyClone	Member of advisory board, consulenze, Trainer at sponsored educational events, Received grants for research activities
Mario Rizzetto	MSD – Janssen – Roche	Member of advisory board
Stefano Vella	Merck & Co. Gilead Sciences J&J	Member of International Scientific advisory board Participation in sponsored educational event

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ITEM 6	PUBLISHING INDEPENDENCE	SCORE 11	75%

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