GRP-041

Collection and analysis of adverse effects and co-medications for outpatients receiving boceprevir- or telaprevir-based treatment for chronic hepatitis C

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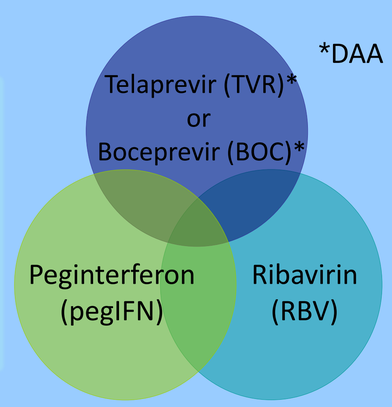
1 Background / Objectives

The current standard of care for chronic hepatitis C virus genotype 1 infection is a triple therapy which :

- ✓ Includes a direct-acting antiviral (DAA) : a protease inhibitor (PI), either telaprevir (TVR) or boceprevir (BOC)
- ✓ Produces better viral response rates, but increases risks of adverse drug reactions (ADRs) and drug-drug interactions (DDIs).



These drugs were introduced in mid-2011. As there is little information available about the results of taking of these drugs, we intended, with this study :

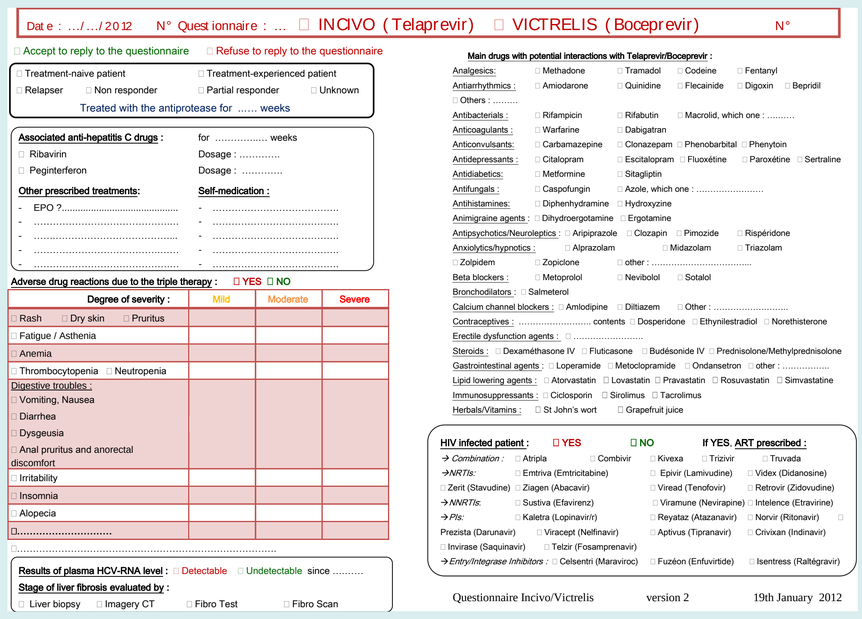
- ➢ To encourage patients to provide feedback on the ADRs and to communicate on potential problems
- ➢ To follow up known DDIs[3]
- ➢ To adapt pharmaceutical advice.

2 Method

- Hospital pharmacists educated themselves about adverse effects and drugs that are commonly associated with clinically significant DDIs.
- A questionnaire was developed to pick up ADRs and to facilitate the identification of DDIs. To support this effort, SPCs and an on-line searchable database of HCV drug interactions[3] supported by the University of Liverpool were used.

  Their routes of metabolism and transport predispose TVR and BOC to drug interactions : both agents are substrates and potent inhibitors of cytochrome CYP 450 3A4 and glycoprotein P-gp.
- Based on this questionnaire validated by doctors, guided pharmaceutical interviews were conducted between January and April 2012. Patients were informed of the process and gave their consent before answering the questionnaire. Hospital pharmacists :
  - ✓ conducted a thorough investigation with outpatients. Each time drugs were dispensed, they could speak about the difficulties, potential adverse effects and the use of prescription, over-the-counter and herbal drugs.
  - ✓ collected adverse effects which had a detrimental impact on quality of life and evaluated potential for DDIs before dispensing the HCV PI.
- Data collected has been consolidated and analysed by hospital pharmacists.

Questionnaire



Date : …/…/ 2012 N° Questionnaire : … ☐ INCIVO (Telaprevir) ☐ VICTRELIS (Boceprevir) N°

☐ Accept to reply to the questionnaire ☐ Refuse to reply to the questionnaire

☐ Treatment-naive patient ☐ Treatment-experienced patient
☐ Relapser ☐ Non responder ☐ Partial responder ☐ Unknown
Treated with the antiprotease for …… weeks

Associated anti-hepatitis C drugs : for …… weeks
☐ Ribavirin Dosage : ……
☐ Peginterferon Dosage : ……

Other prescribed treatments: Self-medication :
- EPO ?…… - ……
- …… - ……
- …… - ……
- …… - ……
- …… - ……

Adverse drug reactions due to the triple therapy : ☐ YES ☐ NO

Degree of severity :	Mild	Moderate	Severe
☐ Rash ☐ Dry skin ☐ Pruritus			
☐ Fatigue / Asthenia			
☐ Anemia			
☐ Thrombocytopenia ☐ Neutropenia			
Digestive troubles : ☐ Vomiting, Nausea ☐ Diarrhea ☐ Dysgeusia ☐ Anal pruritus and anorectal discomfort			
☐ Irritability			
☐ Insomnia			
☐ Alopecia			
☐……			

……

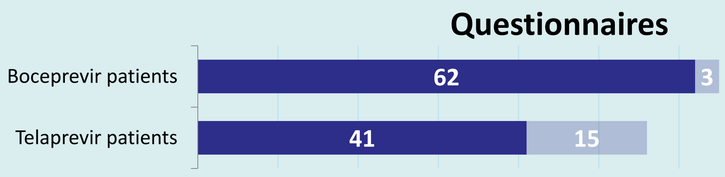
Results of plasma HCV-RNA level : ☐ Detectable ☐ Undetectable since ……
Stage of liver fibrosis evaluated by :
☐ Liver biopsy ☐ Imagery CT ☐ Fibro Test ☐ Fibro Scan

Main drugs with potential interactions with Telaprevir/Boceprevir :
Analgesics: ☐ Methadone ☐ Tramadol ☐ Codeine ☐ Fentanyl
Antiarrhythmics : ☐ Amiodarone ☐ Quinidine ☐ Flecainide ☐ Digoxin ☐ Bepridil ☐ Others : ……
Antibacterials : ☐ Rifampicin ☐ Rifabutin ☐ Macrolid, which one : ……
Anticoagulants : ☐ Warfarine ☐ Dabigatran
Anticonvulsants: ☐ Carbamazepine ☐ Clonazepam ☐ Phenobarbital ☐ Phenytoin
Antidepressants : ☐ Citalopram ☐ Escitalopram ☐ Fluoxétine ☐ Paroxétine ☐ Sertraline
Antidiabetics: ☐ Metformine ☐ Sitagliptin
Antifungals : ☐ Caspofungin ☐ Azole, which one : ……
Antihistamines: ☐ Diphenhydramine ☐ Hydroxyzine
Animigraine agents : ☐ Dihydroergotamine ☐ Ergotamine
Antipsychotics/Neuroleptics : ☐ Aripiprazole ☐ Clozapin ☐ Pimozide ☐ Rispéridone
Anxiolytics/hypnotics : ☐ Alprazolam ☐ Midazolam ☐ Triazolam ☐ Zolpidem ☐ Zopiclone ☐ other : ……
Beta blockers : ☐ Metoprolol ☐ Nevibolol ☐ Sotalol
Bronchodilators : ☐ Salmeterol
Calcium channel blockers : ☐ Amlodipine ☐ Diltiazem ☐ Other : ……
Contraceptives : …… contents ☐ Dosperidone ☐ Ethynilestradiol ☐ Norethisterone
Erectile dysfunction agents : ☐ ……
Steroids : ☐ Dexaméthasone IV ☐ Fluticasone ☐ Budésonide IV ☐ Prednisolone/Methylprednisolone
Gastrointestinal agents : ☐ Loperamide ☐ Metoclopramide ☐ Ondansetron ☐ other : ……
Lipid lowering agents : ☐ Atorvastatin ☐ Lovastatin ☐ Pravastatin ☐ Rosuvastatin ☐ Simvastatine
Immunosuppressants : ☐ Ciclosporin ☐ Sirolimus ☐ Tacrolimus
Herbals/Vitamins : ☐ St John's wort ☐ Grapefruit juice

HIV infected patient : ☐ YES ☐ NO If YES, ART prescribed :
→ *Combination :* ☐ Atripla ☐ Combivir ☐ Kivexa ☐ Trizivir ☐ Truvada
→ *NRTIs:* ☐ Emtriva (Emtricitabine) ☐ Epivir (Lamivudine) ☐ Videx (Didanosine) ☐ Zerit (Stavudine) ☐ Ziagen (Abacavir) ☐ Viread (Tenofovir) ☐ Retrovir (Zidovudine)
→ *NNRTIs:* ☐ Sustiva (Efavirenz) ☐ Viramune (Nevirapine) ☐ Intelence (Etravirine)
→ *PIs:* ☐ Kaletra (Lopinavir/r) ☐ Reyataz (Atazanavir) ☐ Norvir (Ritonavir) ☐ Prezista (Darunavir) ☐ Viracept (Nelfinavir) ☐ Aptivus (Tipranavir) ☐ Crivixan (Indinavir) ☐ Invirase (Saquinavir) ☐ Telzir (Fosamprenavir)
→ *Entry/Integrase Inhibitors :* ☐ Celsentri (Maraviroc) ☐ Fuzéon (Enfuvirtide) ☐ Isentress (Raltégravir)

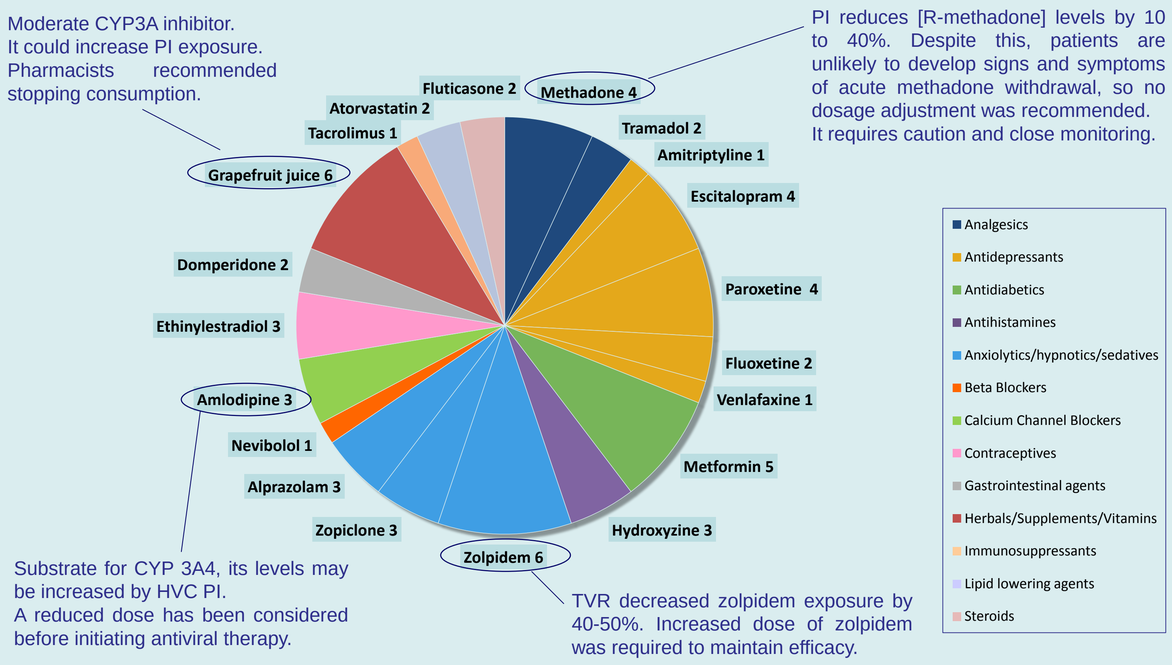
Questionnaire Incivo/Victrelis version 2 19th January 2012

3 Results



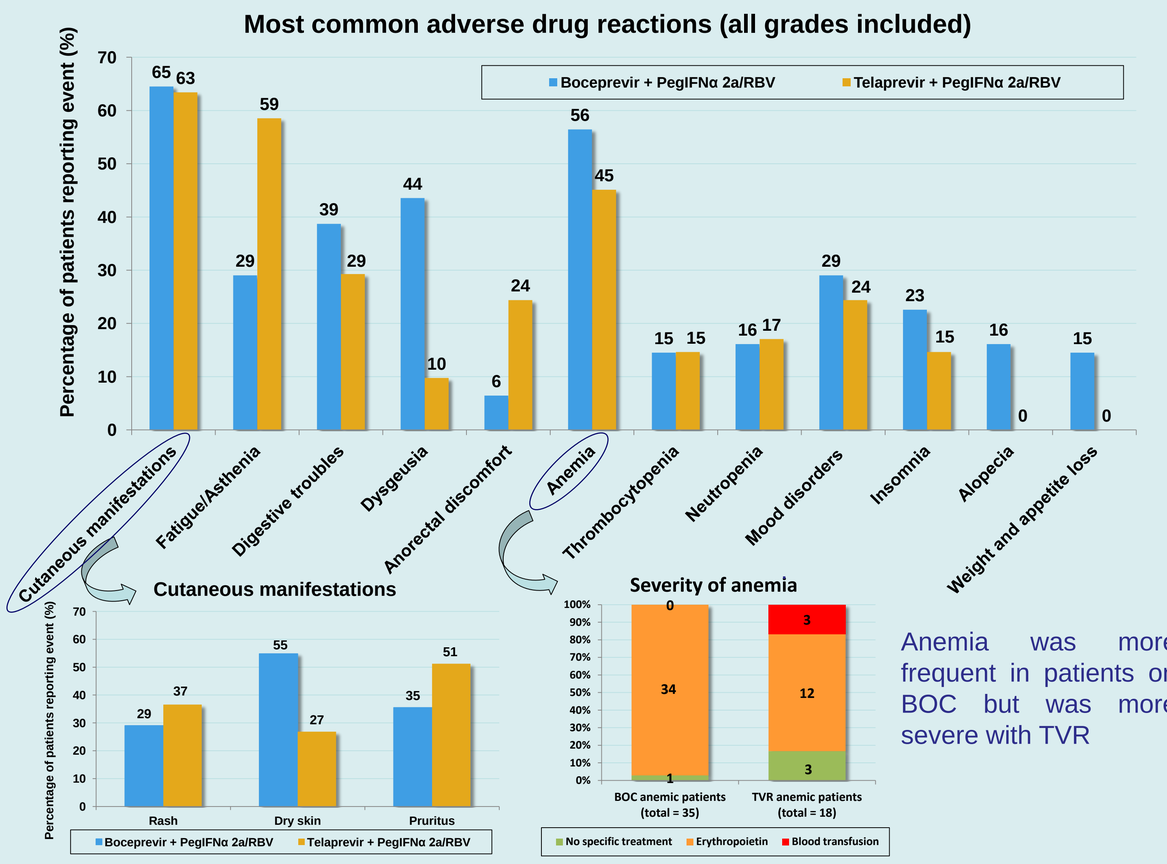
Drug interactions

- 58 potential interactions were identified.
- Risks and benefits of continuing, changing, or discontinuing these medications were considered.



Adverse Drug Reactions

- All patients had ADRs like those reported in SPCs[1,2] :



Anemia was more frequent in patients on BOC but was more severe with TVR

- The most common ADRs were anemia (52% of patients) and cutaneous manifestations (65%), especially dry skin (44%)
- Fatigue, rash and pruritus were more frequent with TVR patients.
- Some ADRs were reported almost exclusively by BOC patients : dysgeusia, alopecia and weight and appetite loss.

4 Conclusion

- Interviews were an important prevention strategy for ADRs and DDIs :
  - ✓ They enabled patients to talk about their ADRs and to express feelings on difficulties faced during their treatment. Hospital pharmacists gave them, in response, moral support and adapted the advice they administered.
  - ✓ They enabled hospital pharmacists to identify DDIs, to consider potential risks and to raise patients' awareness on potential DDIs. Some significant DDIs reported to doctors led to prescription changes.
- Finally, most serious ADRs were reported to health authorities in order to improve the monitoring of risks related to these new drugs.

5 References

1. Summary of product characteristics (SPC) of telaprevir (Incivo®), available on the European Medicines Agency website: http://www.ema.europa.eu
2. Summary of product characteristics (SPC) of boceprevir (Victrelis®), available on the European Medicines Agency website: http://www.ema.europa.eu
3. The hepatitis drug interactions website available at: http://www.hep-druginteractions.org

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