Infliximab: Time-Weighted Bayesian Estimation

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Introduction: Time-Weighted Bayesian Estimation

Infliximab Pharmacokinetic Model

Population specifications

All patients weigh 70 kg. All patients have a baseline albumin of 4 g/dL.

There are 12 seed individuals:

1. ADA onset = 154 days, final albumin = 3 g/dL
2. ADA onset = 154 days, final albumin = 4 g/dL
3. ADA onset = 154 days, final albumin = 5 g/dL
4. ADA onset = 294 days, final albumin = 3 g/dL
5. ADA onset = 294 days, final albumin = 4 g/dL
6. ADA onset = 294 days, final albumin = 5 g/dL
7. ADA onset = 462 days, final albumin = 3 g/dL
8. ADA onset = 462 days, final albumin = 4 g/dL
9. ADA onset = 462 days, final albumin = 5 g/dL
10. ADA onset = 646 days, final albumin = 3 g/dL
11. ADA onset = 646 days, final albumin = 4 g/dL
12. ADA onset = 646 days, final albumin = 5 g/dL

Between time = 0 (baseline) and time = 546 (final), patient albumin changes in a linear sine wave fashion (amplitude = 0.1, frequency = 60 days, phase = 0)

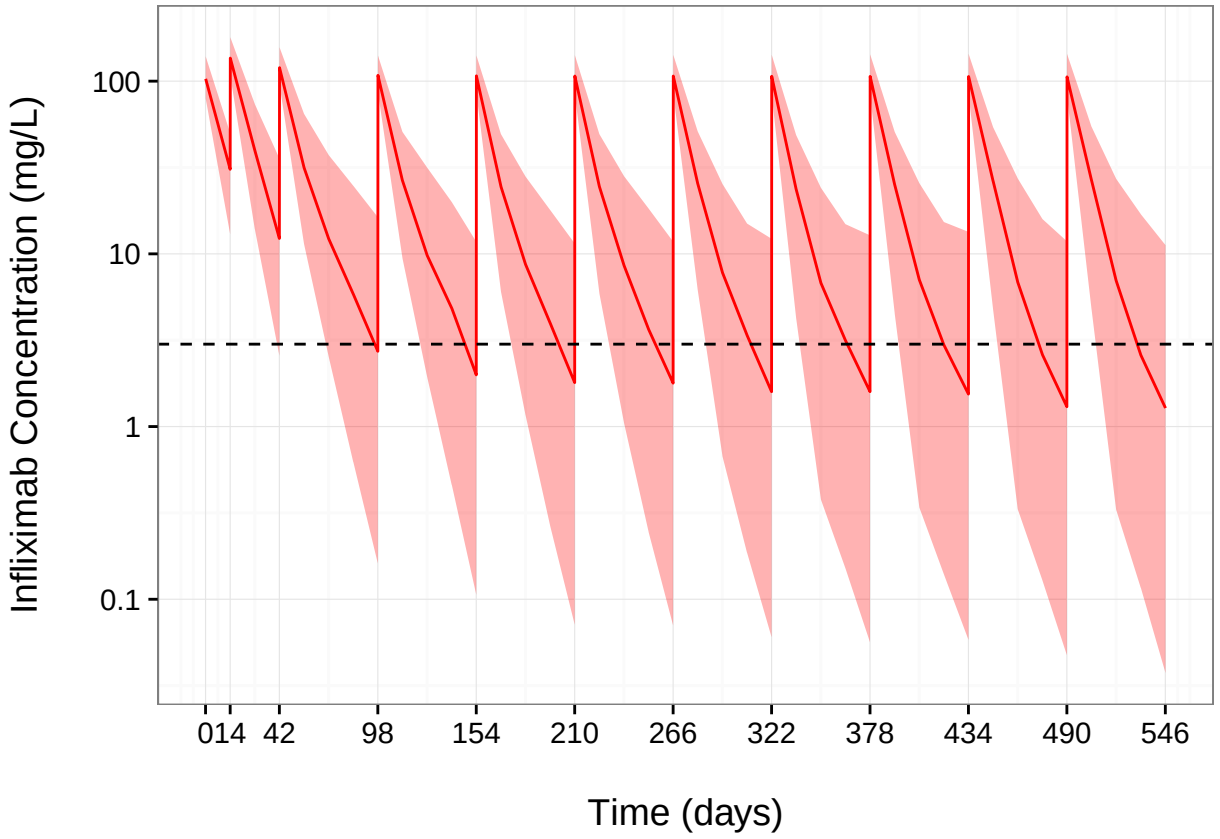
Random effect values for V1, Q and V2 change linearly between time = 0 and time = 546. CL random effect does not change as this parameter holds ADA and albumin covariate effects.

Dosing and Sampling Specifications

1. Simulations run from time = 0 to time = 546 days (approximately 18 months)
2. There are 4 sampling intervals:
    - Sampling interval 1; 0 to 98 days
    - Sampling interval 2; 98 to 210 days
    - Sampling interval 3; 210 to 378 days
    - Sampling interval 4; 378 to 546 days
3. Trough concentrations are sampled at the end of each sampling interval, i.e., time = 98, 210, 378 and 546 days since first dose
4. There are 2 or 3 2-hour infliximab infusions administered in each sampling interval
    - Sampling interval 1; 0, 14 and 42 days
    - Sampling interval 2; 98 and 154 days
    - Sampling interval 3; 210, 266 and 322 days
    - Sampling interval 4; 378, 434 and 490 days

Label Scenario

Every patient receives a 5 mg/kg dose of infliximab at every infusion time (i.e., 350 mg infused over 2 hours)



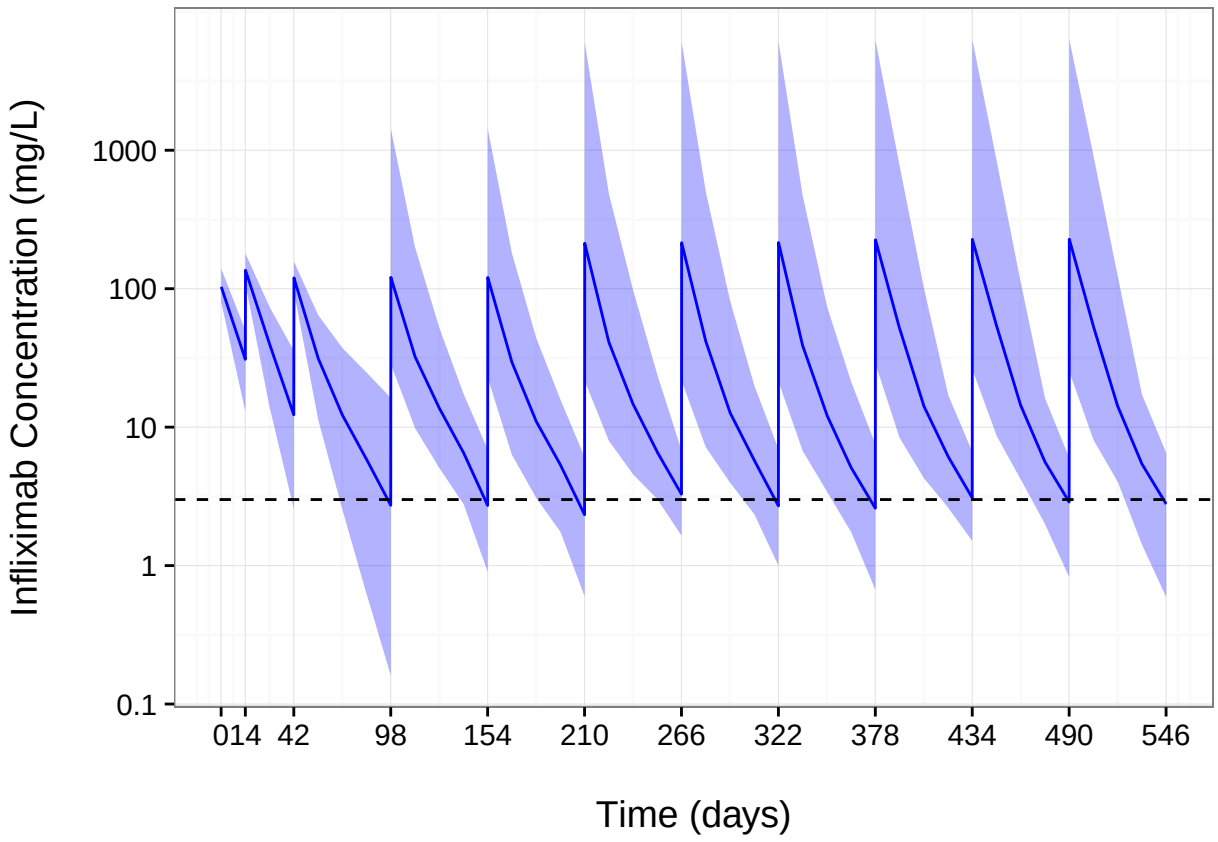
For each individual, the time spent under the target trough concentration (3 mg/L) for the entire 546 day period was calculated.

```
##   time    median   stat.95lo stat.95hi
## 1   98  2.758075 0.002151698  30.78425
## 2  210 19.681735 0.002151698  95.91614
## 3  378 55.786270 0.002151698 207.73028
## 4  546 99.971579 0.002257994 328.09556
```

Clinical Scenario

Scenario where every patient receives a 5 mg/kg dose of infliximab for every infusion time in the first sampling interval (i.e., at 0, 14 and 42 days). Then:

- Trough concentration at time = 98 days is sampled (DV)
- Dose for the next sampling interval is determined as:
  - If a sample < trough target OR sample >= trough upper (5 mg/L) then the new dose will be equal to (trough target/sample)*previous dose
  - If a sample is within the pre-specified range, then the patient continues with the previous dose
- Cycle is repeated at sampling times = 210 and 378 days



We can see a significant improvement in the proportion of people who are achieving constant concentrations above the target trough (median line is predominantly above the line in the clinical scenario compared to the label scenario).

Calculate time spent under the target trough:

```
##   time    median   stat.95lo stat.95hi
## 1   98  2.758075 0.002151698  30.78425
## 2  210 16.729208 0.002332002  71.74241
## 3  378 28.499920 0.002550388  90.43065
## 4  546 43.568000 0.239772690 117.71650
```

The median time spent under the target trough at time = 546 days in the clinical scenario is half compared to the label scenario.

Summarise the amount of drug administered over the 546 day period:

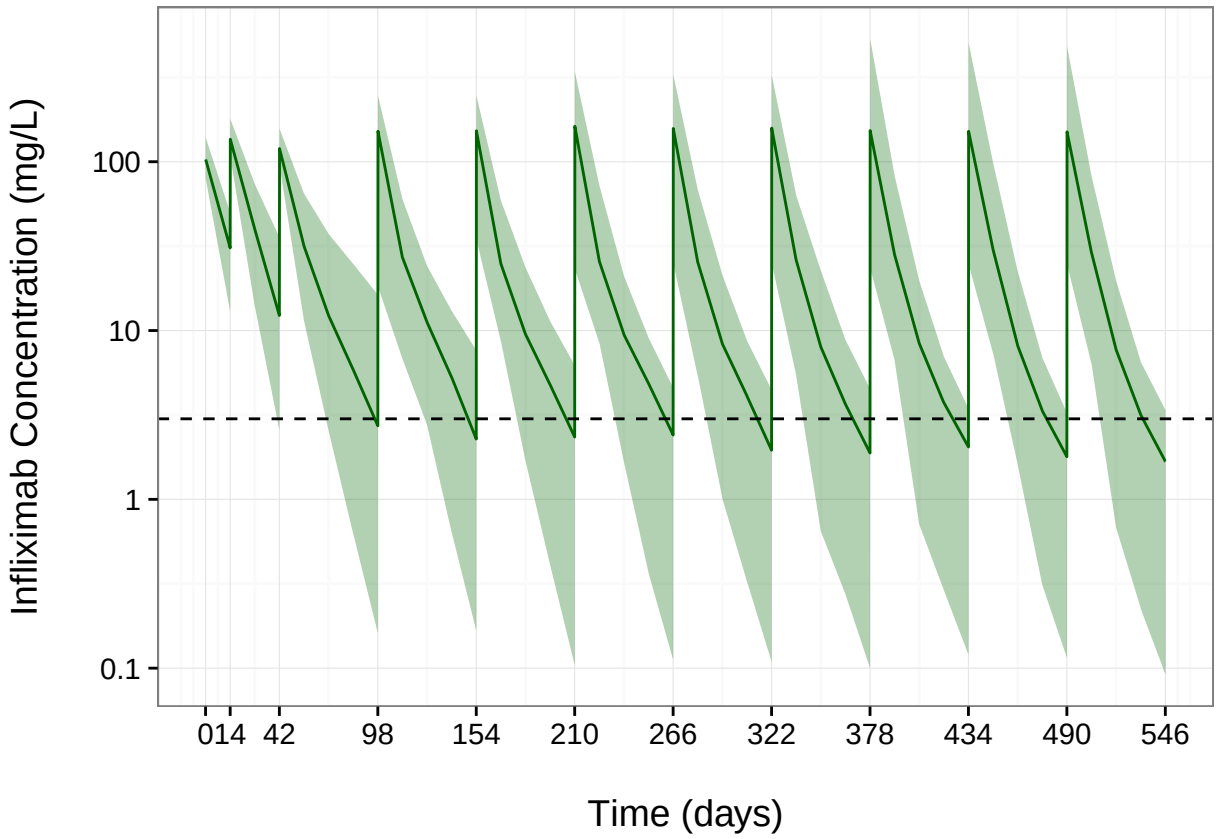
```
##    .id   median stat.95lo stat.95hi
## 1 <NA> 6595.479  1753.723  112908.1
```

Bayesian Estimation and Dose Optimisation Scenarios

No Time-Weighting, All Covariate Information is available

Scenario where every patient receives a 5 mg/kg dose of infliximab for every infusion time in the first sampling interval (i.e., at 0, 14 and 42 days). Then:

- Trough concentration at time = 98 days is sampled (DV)
- Individual values for pharmacokinetic parameters are obtained from empirical Bayes estimates using known administered doses, the sample, and covariate information at time = 0 and the sampling time
- Doses for the next sampling interval are determined by maximum likelihood estimation (minimise the error between trough concentration given optimised doses and the target trough concentration)
  - Optimised doses for the next sampling interval are allowed to be different
  - Initial estimates for doses are obtained by using the method described earlier in "Clinical Scenario"
  - If an initial estimate for a dose was greater than 1,000,000 mg - then doses were not optimised for the patient and they were just administered 1,000,000 mg
- Cycle is repeated at sampling times = 210 and 378 days
  - Bayes estimates obtained from subsequent sampling intervals are based on all previous samples, not just the most recent one



Calculate time spent under the target trough:

```
##   time    median   stat.95lo stat.95hi
## 1   98  2.758075 0.002151698  30.78425
## 2  210 15.323527 0.002151698  90.14727
## 3  378 38.159847 0.002254791 194.31325
## 4  546 67.921278 0.379075782 281.22237
```

Bayesian guided dosing does not appear to be better compared to the "Clinical Scenario" in terms of maintaining trough concentrations above the target. However, is an improvement on current label recommendations.

Summarise the amount of drug administered over the 546 day period:

```
##    .id   median stat.95lo stat.95hi
## 1 <NA> 5261.153  1728.781  10881.25
```

However, Bayesian guided dosing appears to use less drug than the “clinical scenario.”